ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 773

[OPTS-47004; TSH-FRL 1809-7]

Dichloromethane, Nitrobenzene and 1, 1, 1-Trichloroethane; Proposed Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing that manufacturers and processors of dichloromethane, nitrobenzene, and 1,1,1-trichloroethane test these chemicals for health and environmental effects. The Interagency Testing Committee recommended that these chemicals be given priority consideration for testing by EPA. EPA has considered the need to test these chemicals and has made the necessary statutory findings to require testing. The rule would require manufacturers and processors to test these chemicals according to test standards EPA has adopted.

DATES: Please submit written comments on or before August 30, 1981. The comment period for this rule is longer than normal to permit comment on the application of environmental test standards scheduled to be published in July 1981. EPA will hold a public meeting for this rule in Washington, D.C. For further information on arranging to speak at the meeting see section X. of this preamble.

ADDRESSES: Please address your comments to Document Control Officer, Management Support Division (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, 401 M St. SW., Washington, DC 20460.

Please include the document control number OPTS-47000 on all of your comments.

FOR FURTHER INFORMATION CONTACT: John B. Ritch, Jr., Industry Assistance Office, (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm 511 East Tower, 401 M St. SW., Washington, DC 20460, Toll-free: (800-424-9065), In Washington, D.C.: (544-1404), Outside the USA: (Operator-202-544-1404).

The support documents referred to in this preamble are available on request from the Industry Assistance Office.

SUPPLEMENTARY INFORMATION:

I. Introduction

This proposal is part of an ongoing EPA program to require testing of chemical substances. This program implements section 4 of the Toxic Substances Control Act (TSCA, Pub. L. 94-469, 90 Stat. 2003, 2601) which reflects the U.S. policy that adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment and that the development of such data should be the responsibility of those who manufacture and process such chemical substances and mixtures [TSCA section 2(b)(1)].

Section 4 of TSCA authorizes the Administrator of the Environmental Protection Agency (EPA) to require manufacturers (including importers) and processors of identified chemical substances and mixtures to test the chemicals in accordance with applicable EPA test rules [section 4 (a) and (b)]. TSCA requires that each section 4(a) test rule: identify the chemical substances and mixtures for which testing is being required, provide standards for the development of test data, and designate deadlines for the submission of data development in response to the rule [section 4(b)(1)].

In order to require that a chemical be tested, the EPA Administrator must make three findings relating to the chemical's risk or exposure potential, the insufficiency of data available to EPA, and the need to test. These findings are explained in subsequent sections of this preamble.

Section 4(e) of TSCA established an Interagency Testing Committee (ITC) to recommend to EPA a list of chemicals to be considered for testing. The ITC may designate up to 50 entries at any one time for priority consideration by EPA. At the present time the list contains 45 designations. TSCA requires EPA to respond to such designations within 12 months of the date they are made either by initiating rulemaking under section 4(a) or publishing in the Federal Register reasons for not initiating rulemaking.

Today under section 4(a), EPA is proposing health and environmental effects testing requirements for three chemicals: dichloromethane (methylene chloride), 1,1,1-trichloroethane (methyl chloroform), and nitrobenzene. Today's notice constitutes EPA's response to the ITC recommendation that the Agency initiate rulemaking for these three chemicals. These proposed rules, however, do not require testing for all effects recommended by the ITC. This notice and accompanying support documents, which are available from the EPA Industry Assistance Office at the address listed above, explain EPA's basis for believing that the required findings can be made for certain effects and its reasons for not proposing to require testing for other effects recommended for testing by the ITC.

The Agency's first proposed test rule package, published in the Federal Register of July 18, 1980 (45 FR 48510), discusses the implementation of section 4 of TSCA and several general issues which are applicable to today's test rule. The issues of particular interest are: the Agency's position on existing or required test standards; the effective period of a rule; testing responsibilities; exemptions; reporting requirements and deadlines for subchronic, reproductive and teratogenicity health effects testing; and the Agency's policy regarding selection of test substances for test rules.

Although comments on these issues are not being solicited today, EPA will consider any comments submitted on these issues insofar as they apply to testing proposed in today's notice.

In response to concern about the time and level of resources required to prepare the first test rule package, and in light of a court decision finding inadequate EPA's reasons for not proposing test rules within 12 months of receiving certain ITC recommendations, the Agency has substantially changed its approach to promulgating test rules. The new approach involves a more restricted literature search and the development of less detailed support documents. Support documents will be written for the sole purpose of setting forth the technical analysis needed to make the statutory findings. They will not attempt to provide a comprehensive assessment of the chemical or a review of all published literature pertaining to that chemical.

A. Explanation of Section 4(a)(1)(A) Findings

Section 4(a) provides the Administrator of EPA two complementary means to require manufacturers and processors to test chemicals that may be hazardous to human health or the environment. The first means for requiring testing is a set of legal findings that is based on information about the potential risk of the chemical [section 4(a)(1)[A] findings]. The second is a set of findings based on information showing substantial production and substantial human exposure or environmental release of the chemical [section 4(a)(1)(B) findings].

Section 4(a)(1)(A) authorizes EPA to require testing of a chemical substance to develop health and environmental data if the Agency finds that:

(1)(A)(i) The manufacture, distribution in commerce, processing, use, or

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disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment.

(ii) There are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) Testing of such substance or mixture with respect to such effects is necessary to develop such data.

This discussion summarizes briefly EPA's approach to each of the findings EPA must make before requiring testing under this provision. A more detailed explanation of EPA's rationale for interpretation of the finding is included in EPA's first proposed test rule published in the Federal Register of July 18, 1980 (45 FR 48528).

May present an unreasonable risk. EPA uses the term "risk" to include both hazard and exposure potential. Making this finding involves a consideration of several factors, namely, that the chemical (1) may present a hazard, (2) may present a risk, and (3) may present an unreasonable risk.

EPA will consider a variety of factors to suggest the potential health or environmental hazard of a substance. Such factors may include evidence on one adverse effect which may suggest that another adverse effect may occur, knowledge of a chemical's physical and chemical properties, structural relationships to other chemicals with demonstrated adverse effects, data from inconclusive tests, and case history data.

In determining that a chemical may present a risk, EPA must consider both the potential hazard and the potential for human or environmental exposure. However, section 4(a)(1)(A) focuses on those situations in which EPA has a basis for suspecting toxicity, and reflects the fact that a potential for risk may be significant even when exposure is low. Therefore, to make the "may present a risk" finding under section 4(a)(1)(A), it is sufficient for the Agency to show that there is a reasonable likelihood that exposure may arise because of activities associated with the manufacturing, processing, distribution, use or disposal of the chemical. Where monitoring or other specific exposure information is unavailable, the Agency will rely upon reasonable conclusions about exposure potential.

EPA believes that the finding that a substance may present an unreasonable risk contemplates a process of balancing the potential severity of harm from the chemical against the effects of the proposed regulatory action on the availability of benefits of the chemical. It is clear that Congress intended the stringency of this test to vary according to the nature of the action. EPA has proposed pursuing the following policy for the purpose of section 4(a)(1)(A)(i).

If there is substantial evidence that exposure to a chemical may lead to a serious health effect, including a possible increase in mortality, or adverse environmental effects, and that humans or the environment may be exposed to the chemical, EPA will presume that the activities in question (manufacturing, processing, using, transporting, disposing) "may present an unreasonable risk" unless the rule is likely to result in a significant loss to society of the benefits of the substance. In the latter instances, if EPA's analysis shows that the costs of testing may cause manufacturers or processors to cease or severely restrict their commercial activities, EPA will weigh this potential adverse impact against the benefits of testing before presuming that the chemical may present an unreasonable risk.

See EPA's first proposed test rule published in the Federal Register of July 18, 1980, (45 FR 48528), for further discussion of this subject.

Insufficiency of data. The initial step in EPA's approach to this finding is to determine whether studies have been done for the effects under consideration. This effort mainly involves review of existing literature. Next, EPA critically evaluates the design, execution and results of each relevant study to determine whether the study alone, or in combination with others, provides sufficient data to assess the chemical's hazards; that is, does the available information provide the basis for defining the hazard component of a decision whether the chemical does or does not present an unreasonable risk? When this analysis is done in conjunction with the determination that the chemical may present an unreasonable risk, the combined effect of the section 4(a)(1)(A)(i) and 4(a)(1)(A)(ii) findings is the determination that existing information is sufficient to raise the question of potential risk but insufficient to resolve it.

EPA does not require that existing studies meet current EPA test standards in order to be accepted as sufficient. In deciding whether it is necessary to seek further testing for effects for which some data exist, EPA has considered such factors as the benefits of obtaining more data and greater certainty, the likelihood that additional testing would resolve any uncertainties, the cost and economic impact of new testing, the nature of the effects of concern and the likely importance of those effects relative to others already adequately characterized, in defining the needs for control of exposure to the chemical in question. When EPA does conclude that the data are insufficient and more testing is needed, it may be because the studies that have been completed have resulted in equivocal results, or because the existing studies, whether of good or bad quality, do not furnish enough information for EPA to judge the magnitude of risk to populations that are or may be exposed to the chemical or to estimate a level below which the risk can be reduced to a reasonable level.

Necessity for testing. The first aspect of this finding will largely flow from the previous determinations that there are insufficient data and experience to reliably determine or predict the chemical's effects and, where EPA is proceeding under section 4(a)(1)(A), that there is a basis for concern as to the possibility of such risks.

In addition, the Agency must take into consideration ongoing testing of a chemical in determining whether additional testing should be required. In order to do that, EPA examines the protocol and any interim data results of each relevant ongoing study known to the Agency to decide whether the study is likely to produce data which would obviate the need for further testing. The same considerations used by the Agency in evaluating whether there are sufficient data and experience to assess the chemical have been used to evaluate the adequacy of ongoing testing. Where EPA concludes that the ongoing study is likely to meet its needs, there is no need to require additional testing. However, if the final data ultimately generated by the ongoing study do not allow EPA to carry out a reliable risk assessment, EPA at that time will reconsider its decision not to propose a rule for the effect under consideration. Where EPA's review of an ongoing study indicates that serious defects in the design or execution of the study already exist, and are likely to prevent an adequate assessment of the risk upon receipt of the final data, EPA may propose additional testing immediately.

After concluding that there is a need to develop data, EPA must also evaluate whether testing is capable of developing the necessary information. Even if the Agency finds that a chemical may pose a risk from a particular effect, and that there are insufficient data and experience, EPA cannot require a chemical to be tested if no testing methodology exists which would lead to the production of the necessary data, or if, for example, a suitable cohort for an

This is the policy being proposed

epidemiology study cannot be identified. The publication of a generic section 4(a) test standard for a particular effect constitutes EPA's finding that tests conducted according to that standard generally are capable of providing the needed data. Alternatively, EPA may propose a chemical-specific standard for a particular effect without addressing the broader question of its application as a "generic" test standard.

B. Explanation of Section 4(a)(1)(B) Findings.

Section 4(a)(1)(B) authorizes EPA to require testing of a chemical substance to develop health and environmental data if the Agency finds that:

(1)(B)(i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture;

(ii) There are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted; and

(iii) Testing of such substance or mixture with respect to such effects is necessary to develop such data.

This discussion summarizes EPA's approach to making the first of the three findings listed above. Findings 4(a)(1)(B)(ii) and (iii) are identical to findings 4(a)(1)(A) (ii) and (iii) which were discussed in the previous section.

In contrast to the first finding required by section 4(a)(1)(A) which requires EPA to consider the potential of a chemical to pose an unreasonable risk to human health or the environment, section 4(a)(1)(B)(i) requires EPA to consider only quantity of production and potential exposure or release.

EPA is not proposing generally applicable criteria for making section 4(a)(1)(B)(i) findings in this rulemaking. It is the Agency's view that establishment of strict numerical definitions of substantial production, substantial exposure or release, or significant exposure is neither feasible nor desirable at this stage of implementing section 4 of TSCA. Rather, it is EPA's intention to make judgments on these factors on a case-by-case basis, at least until some additional experience is gained. The Agency seeks public comments on this approach and any suggestions of criteria that might be considered for future rulemaking. As is discussed in the individual chemical sections, it is the Agency's view that all three chemicals in this rulemaking clearly would meet any reasonable definition of substantial production, since they are manufactured in quantities of hundreds of millions of pounds per year. Similarly, large portions of the dichloromethane and 1,1,1-trichloroethane production are employed in dispersive and consumer uses, resulting in substantial environmental release and human exposure. A 4(a)(1)(A) approach was taken with respect to nitrobenzene's human health effects because human exposure to nitrobenzene is more limited than it is to dichloromethane and 1,1,1-trichloroethane; however, a 4(a)(1)(B)(i) finding for nitrobenzene was made for environmental effects testing.

C. Basis for Determination of Testing Requirements When Rule is Based on Section 4(a)(1)(B) Findings

The effects of concern for section 4 test rules based on section 4(a)(1)(A) findings are identified in the course of making the findings that the chemical may present an unreasonable risk to human health or the environment. Because section 4(a)(1)(B) findings are based solely on production and exposure or release, and because the Congress intended that this section be used to require testing of chemicals having extensive production, exposure, and release even in the absence of existing data providing evidence of those chemicals' potential to cause specific effects, EPA must use a different approach to define the effects of concern for chemicals on which substantial production and exposure or release findings are made.

The Agency has considered a variety of effects for which it believes data generally are needed to perform an adequate assessment of chemicals which are found to have substantial production, human exposure, and environmental release. The effects were selected for their potential to cause or increase the likelihood of significant injury to humans or economically important nonhuman species or to significantly disrupt normal environmental processes.

Each of the chemicals in this rule for which substantial production and exposure or release findings are made (health and environmental effects for dichloromethane and 1,1,1-trichloroethane and environmental effects only for nitrobenzene) was then considered with respect to these effects of concern, the chemicals' known and expected patterns of human exposure and environmental release or transport, and available data to identify those effects for which EPA believes findings can be made under section 4(a)(1)(B)(ii). The likely adequacy of any ongoing testing for these effects and the availability of suitable test methods was then considered in determining whether the section 4(a)(1)(B)(iii) finding could be made.

The specific testing being proposed for each chemical and the Agency's reasons for believing that any existing tests for those effects are inadequate are summarized in the subsequent sections of this Preamble and discussed in greater detail in the accompanying Support Documents for this proposed rulemaking. Also discussed are EPA's reasons for not requiring tests for any specific effects of concern identified by the ITC but not included in today's proposals.

The paragraphs below summarize the Agency's reasons for believing that each of the effects for which testing of one or more chemicals is proposed in this rule under section 4(a)(1)(B) is of concern.

1. *Human health effects*—a. *Acute toxicity: oral, dermal, and inhalation.* Acute toxicity data must be available to assess the potential risk of poisoning due to a single exposure to any given chemical. These studies provide data to determine the median lethal dose (LD_{50}) of the chemical substance and permit estimates of the chemical's toxicity relative to that of other substances. They may also provide data to predict a chemical's mechanism of toxicity, to demonstrate its specific toxic effect on target organs and functions, to determine differences in sensitivity to the substance among species, and to compare toxicities associated with different routes of exposure. In addition, acute tests serve as range-finding tests to determine appropriate doses for subchronic tests.

b. *Acute dermal irritation/corrosion.* Data indicating the capacity of a chemical to cause irritation and/or corrosive effects on the skin of laboratory animals permit an evaluation of the possible hazards to humans which may arise from dermal exposure to a substance. This evaluation is used to guide health and safety practices for the handling of a chemical substance.

c. *Acute eye irritation/corrosion.* Data indicating the capacity of a substance to injure the eye and associated mucous membranes help determine the hazard of a chemical substance which accidentally enters the eye, as may occur during handling of the substance.

d. *Skin sensitization.* Data indicating the capacity of a chemical to induce a state of delayed sensitization when it comes in contact with the skin of laboratory animals help determine the hazard of a chemical substance that comes in contact with the skin, such as

may occur during any activity involving handling of the substance.

e. *Chronic toxicity.* Data from chronic toxicity studies indicate what major toxic effects to expect from repeated long-term exposure to the test substance and what target organs or functions may be affected. These data may also provide information on the delayed effects of chemicals that may be due to bioconcentration of test substances or their metabolities. In certain instances, the reversibility of these effects as well as the rate of absorption, metabolism and excretion of the chemicals may also be determined. Chronic toxicity data help determine the hazard of a chemical substance that is repeatedly ingested, inhaled, or absorbed through the skin, such as may occur during any human activity in proximity to vapors of the chemical, during handling of the substance, or when water contaminated with the substance is drunk.

f. *Mutagenicity.* Data from mutagenicity studies may indicate the capacity of a substance to alter (produce mutations) in the genetic materials of a cell either at the gene or chromosome level. Gene or chromosome mutations may result in effects that are transmitted to future generations. Because some chemicals induce only one type of genetic alteration, test sequences for both gene (point) mutations and chromosomal abberrations are needed. Information indicating a mutagenic consequence is used to assess the potential of a chemical substance to alter genetic information. Congress indicated that mutagencity was a health effect of special concern for regulatory action [TSCA section 4(f)].

g. *Reproduction and teratogenic effects.* Data from reproductive and teratogenicity tests show whether a substance may affect whether humans or animals may bear young and, if they do, whether the fetus or young develop normally. From these tests, specific data can be obtained which indicate the effects of the substance on pregnant females and on male and female reproductive organs, general reproductive performance of both sexes, fertilization, implantation, embryonic tissue differentation and organogenesis, prenatal growth and functional maturation, birth, lactation, maternal care of offspring, postnatal growth, and survival fecundity. Information indicating a reproductive or teratogenic consequence is used to assess the ability of a chemical substance to produce birth defects or impair reproductive functions. Congress indicated that birth defects was a health effect of special concern for regulatory action in TSCA section 4(f).

h. *Oncogenicity.* Data from oncogenicity studies indicate whether a substance is likely to produce tumors in test animals as a result of repeated long-term exposure. Existing tests for mutagenicity are not adequate for a full evaluation of oncongenic potential. Short-term tests are not sensitive to all classes of chemicals and may not predict the oncogenic ability of chemicals, particularly those which act through non-genetic mechanism. Thus, long-term, repeated-dose testing in animals must be performed to throughly evaluate whether or not a chemical may be oncogenic. In addition, past experience with oncogenic studies on animals has confirmed their usefulness in predicting the oncogenicity of such chemicals as vinyl chloride, aflatoxin, and asbestos, which are now widely accepted as human oncogens. Congress indicated that cancer was a health effect of special concern for regulatory action [section 4(f)].

i. *Neurotoxicity.* Data from neurotoxicity studies are necessary to provide information on the ability of a substance to produce acute and chronic neurotoxic effects. However, TSCA test standards for neurotoxicity testing have not yet been developed. Therefore, no neurotoxicity testing will be proposed by EPA at this time.

2. *Environmental effects.* For the three chemicals under consideration, the Agency has determined that all major sectors of the environment (i.e., land, freshwater, saltwater, air) are potentially exposed to each chemical; consequently, effects of concern for the environment include toxicity to freshwater, saltwater, and terrestrial organisms.

a. *Aquatic vertebrates: acute and chronic toxicity.* Fish are of significant commerical and recreational importance to humans. Some of the species most sensitive to toxicant are also of high economic importance (e.g., salmon, trout). Data on both saltwater and freshwater aquatic vertebrates are necessary because there are major physiological differences between saltwater and freshwater organisms. Also, data on both warmwater and coldwater fish are necessary because the sensitivity of fish to a given toxicant may depend markedly on the water temperature to which the fish are adapted.

Acute toxicity data on fish must be available to assess the potential risk of poisoning due to short-term exposure, such as might be encountered during spills or near wastewater outfalls, and to provide data necessary to select dose levels for long-term (chronic) testing. Early life stage or full life cycle toxicity data must be available to determine potential effects resulting from long-term exposure; the early life stage test covers that portion of the life cycle generally shown to be most sensitive to toxicants and therefore functions adequately as a substitute for a full life cycle test.

b. *Aquatic invertebrates: acute and chronic toxicity.* Many aquatic invertebrates are of significant commercial importance to humans, e.g., shrimp, clams, oyster. In addition, many aquatic invertebrate species serve as a food base for higher trophic level organisms (organisms higher in the food chain), including commercially valuable fish and endangered waterfowl. As with aquatic invertebrates, data on both saltwater and freshwater aquatic invertebrates are necessary because there are major physiological differences between saltwater and freshwater organisms.

Acute toxicity data on aquatic invertebrates are necessary to determine the potential risk of poisoning due to short-term exposure such as might be encountered during spills or near wastewater outfalls, and to provide data necessary to select dose levels for long term (chronic) testing. Data from multigeneration toxicity tests are necessary to assess potential effects of long term exposure.

c. *Aquatic plant toxicity.* Algae (free-floating unicellular plants) and vascular aquatic plant life (e.g., seaweed, duckweed) are at the botton of food webs that support all aquatic vertebrates and much terrestial life. In addition, many vascular aquatic plants provide habitats for fish and invertebrates and can play an important role in nutrient recycling.

Both depletion and stimulation of aquatic plant life can present significant environmental problems. Decreased plant production may result in decreased fish production, while excessive stimulation of plant growth can lead to effects which may decrease production of commercially important fish species and decrease the aesthetic and recreational value of a water body.

Data on both algae and vascular plants are necessary because there are major differences between these organisms with respect to phylogeny, habitat, uptake of chemicals, and physiology. Data on both saltwater and freshwater plant species is necessary because chemical transformations can be very different in the two media, and because there are major physiological differences between saltwater and freshwater organisms.

d. *Birds and mammals: acute and chronic toxicity.* Birds and mammals provide important recreational resources for humans and are vital links in maintaining ecological balance. Also, an increasing number of bird and mammal species are being classified as endangered species.

Data on both birds and mammals are necessary because there are major differences between these organisms with respect to phylogeny, reproduction, and physiology. Acute toxicity data on birds and mammals must be available to assess the potential risk of poisoning due to short-term exposure to a chemical such as might be encountered during spills. The acute oral test on laboratory mammals listed under Human Health Testing (section (1)(a)] is acceptable for assessing the acute hazard of toxicants to wild mammals. The acute test on birds is ordinarily a 5-day dietary test to simulate natural exposure. If the test substance is volatile, a single oral dose test is generally more appropriate because maintaining nominal concentrations in the feed would be difficult in the dietary test. Other toxicity tests must be performed to test for potential effects resulting from long-term exposure. The 90-day subchronic test on laboratory mammals listed under Human Health Testing (section (1)(e)] is acceptable for assessing the chronic hazard of toxicants to wild mammals. Long-term testing on birds must include the reproductive phase of the life cycle because it is generally the most sensitive to toxicants.

e. *Terrestrial plants.* Terrestrial plants are of obvious importance to agriculture and forestry. Also, terrestrial plants are at the bottom of the food web that supports most terrestrial life. Terrestrial plants may be exposed to section 4 chemicals through rainfall and contaminated irrigation water.

There are several important plant functions that may be affected by toxicants, including root elongation, seed germination, shoot and leaf growth, and flowering. Impairment of any of these functions may result in death or reduced productivity. Test data must be available to assess potential effects on these functions.

f. *Bioconcentration.* A major potential hazard exists to both the environment and humans from toxicants that concentrate in plant and animal tissues. Organisms that consume plants or other animals with high body burdens of a toxicant may be exposed to concentrations several orders of magnitude above those in the abiotic environment (water, sediment, soil, air). For example, top trophic level carnivorous birds have experienced serious reproductive effects (eggshell thinning) resulting from food chain transport of DDT and other pesticides. Humans are also top level carnivores and therefore may receive very high levels of toxicants that bioconcentrate.

It is also possible that high tissue levels of a toxicant can be rapidly transferred to the same organism's blood stream, resulting in acute or chronic effects. This phenomenon may occur as the animal is rapidly using up its fat reserves, such as occurs when salmon or birds migrate.

For many chemicals, a reasonable prediction of the potential to bioconcentrate can be made by determining the chemical's fat solubility relative to its water solubility. The "octanol/water partition coefficient" is a term used to denote this physicochemical characteristic. It is a measure of solubility in octanol relative to that in water and is usually expressed as the logarithm of the coefficient ("log P_{oct}", "Kow"). The coefficient has been shown to correlate well with indices of bioconcentration determined from actual uptake studies using fish. However, for chemicals that concentrate significantly in tissues other than fat (e.g., muscle), the Log P_{oct} may underestimate actual bioconcentration.

Data are needed on a variety of organisms because bioconcentration potential varies depending on physiological characteristics, feeding behavior, and mode of respiration.

g. *Other effects of concern.* Other effects of concern include toxicity to terrestrial invertebrates, alteration of microorganism functions, and ecosystem effects. No TSCA section 4 test standards are available for these effects and therefore no testing for these effects is being proposed by EPA at this time.

3. *Chemical fate: persistence and transport.* Data are required for environmental persistence and/or transport characteristics that play significant roles in governing chemical fate in compartments of the environment where exposure to humans or other life forms is possible. These data are needed in order to perform a complete assessment of risk posed by a chemical to humans or the environment.

D. Test Standards

The Agency is developing a series of generic standards for development of test data (TSCA, Pub. L 94-469; 90 Stat. 2006; 15 U.S.C. 2603). These standards will then be available to incorporate in specific chemical testing rules as they are issued under section 4 of TSCA. Previously-issued proposals covered the development of data on chronic health effects and Good Laboratory Practices for health effects, published in the Federal Register of May 9, 1979 (44 FR 27334), and also on acute and subchronic toxicity, mutagenic, teratogenic and reproductive effects and metabolism studies published in the Federal Register of July 26, 1979 (44 FR 44054). The Agency proposed standards for development of test data on certain physical and chemical characteristics of substances and Good Laboratory Practices related to environmental effects testing published in the Federal Register of November 21, 1980 (45 FR 77332). The notice covered testing for Density/Relative Density, Melting Temperature, Vapor Pressure, Octanol/Water Partition Coefficient and Soil Thin Layer Chromatography.

Today's test rule proposes that dichloromethane, nitrobenzene, and 1,1,1-trichloroethane be tested for various environmental effects. Test standards for these effects were scheduled to be published prior to this proposal; however, publication of these standards has been delayed several months and is now scheduled for July 1981. Because of this delay, the comment period for this rule has been extended to August 30 to permit comment on the applicability of the environmental standards to this rule.

The EPA has been a full and regular partner in extensive international consultations and negotiations in the Organisation for Economic Cooperation and Development (OECD) during the development of its chemical testing and other requirements under TSCA. U.S. experts, along with those of other OECD member states, have worked since 1977 to develop agreed chemical testing guidelines and good laboratory practices. The Agency places a high priority on these activities because of benefits both for international chemical trade and for more effective health and environmental protection.

In developing test standards for section 4, EPA will pursue consistency with OECD test guidelines, and a concerted effort will be made to incorporate OECD wording. However, where EPA language provides a substantial improvement or is necessary to comply with a U.S. statutory or judicial requirement, it will be used. Additions to, or deletions from, the OECD Guidelines will be strictly limited and a rationale provided in such cases. Additions will generally be limited to suggested or preferred criteria or to explanatory (rather than required) phrases such that the basic requirements cannot be construed as being different.

E. Testing Being Performed by EPA

EPA will perform initial mutagenicity testing and testing on various environmental effects and chemical fate processes for which TSCA section 4 test standards will not be available in the near future. The environmental effects and chemical fate tests which EPA will perform include acute and chronic toxicity to coldwater saltwater vertebrates, full life cycle tests on terrestrial plants, and tests for chemical persistence.

EPA does not intend to perform such tests routinely because, as TSCA section 2 states, the development of data on the effects of commercial chemicals should be the responsibliity of the manufacturers and processors of those chemicals. EPA is making an exception to this general policy in this case as it did for mutagenicity testing proposed for chloromethane and the chlorinated benzenes in the Federal Register of July 18, 1980 (45 FR 48510) because it believes this exception to be in the public interest. This belief rests on these reason: (1) EPA's sponsorship of these tests will contribute to the Agency's development of test standards in these areas; (2) information on these effects is important to the assessment of these chemicals and we believe it is important not to delay testing; and (3) the cost of this testing is relatively low.

In the case of mutagenicity testing, EPA has been unable to develop specific criteria for test sequencing decisions that are suitable for inclusion in section 4 test standards. EPA believes that such criteria are important to insure consistency between various laboratories in their determinations of whether to stop testing or proceed to the next test in the sequence. In addition, EPA has not yet developed test standards to be followed in the gene mutation sequence or the in vivo cytogenetics test for chromosomal aberration. Based on its evaluation of the results of these tests, EPA will decide whether to propose that the final tests of the mutagenicity sequence be performed by industry.

F. Voluntary Testing by Industry

In late February 1981, EPA was approached by representatives of the manufacturers of dichloromethane and 1,1,1-trichloroethane to discuss the possibility of voluntary testing for these substances. This resulted in two meetings (March 16, 1981 and March 25, 1981) to discuss the environmental and health effects testing needs for these two substances. While these meetings were quite productive, and resulted in a useful exchange of ideas and information among the persons in attendance, they have not yet resulted in the development of a voluntary testing program. Should a voluntary testing program be developed for these substances that would satisfy the Agency's need for sufficient data to reasonably predict or determine the effects of the exposure to, or environmental release of these chemcials, EPA will withdraw this proposal insofar as it relates to dichloromethane and 1,1,1-trichloroethane. In addition, these meetings have resulted in the submission of certain health and enviornmental effects testing data by industry that had not previously been submitted to the Agency or evaluated by it. The data submitted to date have been summary in nature and thus could not be adequately evaluated. EPA is attempting to obtain sufficient backup materials relating to these studies to enable it to evaluate their adequacy. Should this evaluation demonstrate that adequate data are available to reasonably predict or determine those effects, EPA will modify this proposal to delete the proposed testing requirements for those effects.

II. Dichloromethane

A. Introduction

Dichloromethane (CH_2Cl_2, methylene chloride, CAS No. 75-09-2) is a clear, colorless, volatile liquid at standard temperature and pressure. Dichloromethane is a high production chemcial (U.S. production in 1979, 634 million pounds). U.S. dichloromethane production in the first 11 months of 1980 showed a sharp decrease, with a production of 537 million pounds projected for the entire year.

Dichloromethane has a variety of uses. Major uses are as a paint-stripping solvent, as a urethane foam-blowing agent, as a vapor-degreasing and dip solvent for metal cleaning and as a solvent for aerosol products.

The manufacturing, processing and use of dichloromethane results in exposure of both workers and consumers. The National Occupational Hazard Survey (NOHS) estimated that approximately 2.5 million persons are exposed to dichloromethane annually in occupational settings. Dichloromethane is also an ingredient in many consumer products: cleaning agent, aerosols, adhesives, paints and paint removers.

The Interagency Testing Committee (ITC) recommended that dichloromethane be tested for carcinogenicity, mutagenicity, teratogenicity, other chronic effects, and environmental effects, and that epidemiology studies be done.

B. Findings

With the exception of subchronic cardiovascular effects, EPA is basing its proposed testing requirements on the authority of section 4(A)(1)(B) of TSCA.

EPA finds that dichloromethane is produced in substantial quantities (634 million pounds/yr), and that its production is expected to increase in the future.

EPA also finds that substantial numbers of persons are exposed to dichloromethane both in occupational settings and as consumers. EPA also finds that there is substantial release to the environment. Of the dichloromethane produced in the U.S., approximately 84% (499 million pounds/yr) is expected to reach the environment.

EPA also finds with respect to he areas listed below that there are insufficient data and experience to determine the effects resulting from the manufacture, processing, distribution in commerce, use, or disposal of dichloromethane, and that testing is necessary to develop such data:

Health effects:
- Acute dermal sensitization
- Reproduction

Environmental effects:

Aquatic vertebrates
- Chronic toxicity

Aquatic invertebrates
- Chronic toxicity

Birds
- Acute toxicity
- Chronic toxicity

Terrestrial plants
- Early seedling growth

Bioconcentration
- Plant uptake/translocation
- Aquatic vertebrate

The proposed testing and reporting requirements for each of these effects are described below. Testing recommended by ITC or identified with an effect of concern, but not proposed above, will be handled as described in the following paragraphs.

EPA is not proposing testing for chemcial fate, acute health effects (except for skin sensitization), chronic effects, teratology, or for certain environmental effects, e.g., acute toxicity to aquatic vertebrates and invertebrates, aquatic invertebrate bioconcentration, toxicity to mammals, seed germination, because it believes that existing information is adequate. EPA will perform testing on some of the environmental effects for which no

standards are available as described in I.E. of this preamble.

Oncogenicity testing of dichloromethane is being performed by the National Cancer Institute (NCI) and the EPA believes that the NCI studies should be sufficient for the Agency's needs; therefore, no additional oncogenicity testing is being proposed at this time.

EPA believes that mutagenicity testing according to a testing sequence would be appropriate, and will perform the initial testing itself because no criteria for progressing from initial tests to higher level tests are available. EPA will propose higher tier tests if needed based on analysis of lower tier results. There are no test standards available for neurobehavioral toxicity so neurobehavioral testing is not proposed at this time. Industry is sponsoring an epidemiology study; therefore, no studies of this type are being proposed at this time.

On the basic of acute toxicity studies in dogs which showed increased arterial pressure and myocardial contractibility and evidence of exposure of large numbers to dichloromethane at levels where effects might occur, EPA finds under section 4(a)(1)(A) that dichloromethane may present an unreasonable risk of adverse cordiovascular effects to humans. EPA also finds that there are insufficient data on the effects to the cardiovascular system of nonacute exposure to dichloromethane and that testing is necessary.

The analysis and findings upon which the above determinations are based are presented in the Dichloromethane Support Document which is available from the Industry Assistance Office.

C. Persons Required to Test

Section 4(b)(3)(B) specifies that the activities for which the Administrator makes section 4(a) findings (manufacturing, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing, distribution, use or disposal. Processors are required to test if the findings are based on processing, distribution, use or disposal.

Because exposure to dichloromethane occurs through several routes, persons who manufacture or process dichloromethane, and those who intend to manufacture or process dichloromethane within the period ending five years beyond the date required for the submission of the last final report of this test rule will be subject to this test rule. Because "manufacture" is defined in section 3(7) of TSCA to include "import," importers of dichloromethane are subject to this rule.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are required to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) specifically provides that any person required to test may apply to EPA for an exemption from that requirement.

EPA is not proposing to require the submission of equivalence data as a condition for exemptions from the proposed testing. As noted below, EPA is interested in evaluating the effects attributable to dichloromethane itself, and has specified a relatively pure grade substance for testing. Please see EPA's proposed statement of exemption policy for more information published in the Federal Register of July 18, 1980 (45 FR 48512).

D. Test Substance

The EPA is proposing that a relatively pure grade of dichloromethane be used as the test substance. The proposed test substance contains no stabilizers. Most commercial grades of dichloromethane contain one or more stabilizers, which may have toxicological effects of their own, making it more difficult to evaluate dichloromethane's toxicity from tests on a technical grade substance. A purity of 99.95% which corresponds to the material used in the NCI bioassay is specified in this rule.

E. Proposed Testing

Because the most common human exposure is expected to be by inhalation of dichloromethane vapors, the route of administration for health effects testing must be by inhalation with the exception of the dermal sensitization study. In the dermal sensitization study the test substance must be injected intradermally because it is highly volatile and would not, therefore, remain on the skin for an adequate period of time if applied topically.

The route of administration for each environmental effects test is specified in the generic test standard for that effect, with exceptions as noted below.

The following are effects of concern discussed in I.C. of this preamble, for which EPA is proposing testing.

1. *Acute effects—dermal sensitization.* The EPA is proposing that an acute dermal sensitization test be conducted in accordance with test standards to be promulgated under 40 CFR 772.112–26. The proposed standard was published in the Federal Register of July 28, 1979 (44 FR 44054).

2. *Subchronic cardiovascular toxicity.* Because there is no generic subchronic cardiovascular test standard available at this time, the Agency is proposing a chemical-specific standard for this test rule which includes the performance of five major tests: right and left heart catheterization; electrocardiographic monitoring; cardiac sensitization studies; determination of carboxyhemoglobin and dichloromethane levels in the blood; and histopathology. Since the heart has both electrical and mechanical functions, all of the above-mentioned procedures are deemed necessary to adequately evaluate the effect of dichloromethane on the cardiovascular systems as explained below.

a. *Cardiac catheterization.* The measurements which are normally taken, during a cardiac catheterization provide functional information involving the chambers and great vessels of the heart. Any deviations from normal will identify functional disturbances caused by subchronic dichloromethane exposure.

b. *Electrocardiographic monitoring.* Changes in the electrocardiogram such as the production of ectopic beats or the appearance of more serious arrhythmias, tachycardia, flutter, fibrillation, will provide information on any disturbance of cardiac rhythm and/or of conduction including the potential presence of ischemic damage to the myocardium.

c. *Cardiac sensitization.* If the administration of normally non-arrhythmogenic doses of epinephrine cause a statistically significant number of aberrations in the electrocardiogram following dichloromethane exposure, then this observation suggests that the threshold for the production of arrhythmias may have been lowered. The highest dose of epinephrine which should be used in any sensitization study is that does which produces ectopic beats or more serious arrhythmias such as tachycardia, fibrillation, flutter. This information is essential to evaluate any potential hazard which may exist due to long-term exposure to dichloromethane, not only for those individuals predisposed to cardiovascular disease or other stress condition but to normal individuals as well.

d. *Analysis of dichloromethane and carboxyhemoglobin levels in the blood.* Dichloromethane is capable of being metabolized to carbon monoxide which

readily combines with hemoglobin to produce carboxyhemoglobin. This substance decreases the oxygen-carrying capacity of the blood and can lead to tissue ischemia at high levels. It is, therefore, important to determine if carboxyhemoglobin levels are significantly increased following exposure to dichloromethane and to determine the potential correlation between the levels of carboxyhemoglobin and the dichloromethane concentration in the blood. Given this information, it may be possible to determine whether or not the cardiovascular changes which may arise are due to the formation of carboxyhemoglobin or, rather, are a direct effect of dichloromethane on the heart or nervous system. Histopathologic changes on the specified tissues will be used to demonstrate: (1) that permanent tissue damage has occurred; (2) that the cells have been injured by the toxic influence, but have not yet been permanently damaged; or (3) that physiological changes in the function of the heart have occurred due to dicholormethane exposure but have not produced concurrent cellular injury or death.

The dog is specified as the test animal for the proposed Subchronic Cardiovascular Test Standard for the following reasons: (1) based on results found in the literature, the dog appears to be more sensitive to the cardiovascular effects of dichloromethane than the rodents; (2) the majority of the existing acute cardiovascular toxicity test data has been determined in the dog; (3) being a proven, reliable model, the dog is used extensively in cardiovascular studies; and (4) the use of a large animal will facilitate the performance of the required tests. Either males or females may be employed; however, testing must be carried out on dogs of one sex to reduce any additional variable.

The Agency proposed an initial test dose of 250 ppm. This choice is based on a study in which a single two-hour exposure of dogs to 500 ppm dichloromethane produced changes in myocardial contractility and mean arterial pressure, induced arrhythmias, and increased carboxyhemoglobin levels in the blood (Adams, 1975, The Effects of carbon monoxide and methylene chloride on the canine heart, Ph.D. Thesis, Texas A&M University). The initial 250 ppm dose was chosen because long-term exposure to 500 ppm may lead to excessive toxicity that may jeopardize test animal survival for the entire test period. Negative results obtained with dichloromethane exposure at this level will obviate the need for further testing. Statistically significant results within the parameters designated in the test standard will necessitate repetition of the entire test procedure at one-half the previous exposure concentration. This procedure must be followed until the analysis of the data ceases to express statistical significance. However, in the event that three exposure levels have been tested and statistically significant changes in the designated parameters are still maintained, testing may be terminated at this point. This proposed study is necessary to determine a "no observable effect level" for dichloromethane, with respect to cardiovascular toxicity. If the data permit, a mathematical extrapolation to a "no observable effect level" should be made.

3. *Reproductive toxicity.* The EPA is proposing that a reproductive effects test be done in accordance with test standards to be promulgated under 40 CFR 772.116–3. The proposed standard was published in the Federal Register of July 26, 1979 (44 FR 44054).

4. *Aquatic vertebrates—chronic toxicity.* The EPA is proposing early life stage toxicity testing on a coldwater and a warmwater freshwater fish species and on a saltwater fish species in accordance with test standards to be proposed in the Federal Register in July, 1981 (see discussion in I.D. of this preamble). The coldwater freshwater species tested must be the rainbow trout (*Salmo gairdneri*) because this species is generally more sensitive to toxicants than the brook trout (*Salvelinus fontinalis*).

5. *Aquatic invertebrates—chronic toxicity.* The EPA is proposing life cycle toxicity testing on a freshwater and saltwater invertebrate in accordance with test standards to be proposed in the Federal Register in July, 1981. The freshwater invertebrate test must be flow-through due to the high volatility of dichloromethane. Evaporation of dichloromethane in the static renewal procedure would result in difficulty in maintaining nominal exposure levels.

6. *Birds—acute toxicity.* The EPA is proposing acute toxicity testing on two species of birds in accordance with proposed FIFRA guidelines published in the Federal Register of July 10, 1978 (43 FR 29696, § 163.71–1). The FIFRA guidelines for acute avian toxicity are being proposed as test standards specific to this chemical in this rule.

7. *Birds—chronic toxicity.* The EPA is proposing reproductive toxicity testing on two species of birds in accordance with the test standards to be proposed in the Federal Register in July, 1981.

Dose level selection is proposed to be made as follows:

High dose (ppm)—0.125 x LD_{10} (in mg/kg) obtained in single oral dose acute toxicity test

Medium dose (ppm)—0.167 x high dose

Low dose (pm)—0.028 x high dose

Also, because dicholormethane is highly volatile, special dietary procedures are proposed.

8. *Terrestrial plants—early seeding growth.* The EPA is proposing early seedling growth testing in accordance with test standards to be proposed in the Federal Register in July 1981. EPA proposes that each species must be tested twice, once using the foliar route of exposure and once using the nutrient medium as the route of exposure, because plants may be exposed by either route and toxicity may be significantly dependent upon the route of exposure.

9. *Bioconcentration—plant uptake/translocation.* The EPA is proposing plant uptake/translocation testing in accordance with test standards to be proposed in the Federal Register in July, 1981. The most sensitive monocot and the most sensitive dicot observed in the early seedling growth test must be tested because high sensitivity may be the result of high rates of uptake, and bioconcentration potential may differ significantly between monocots and dicots. Testing on more species is recommended but not required. Each species must be tested twice, one using the foliar route of exposure and once using the nutrient medium as the route of exposure, because plants may be exposed by either route.

10. *Bioconcentration—aquatic vertebrate.* The EPA is proposing aquatic vertebrate bioconcentration testing in accordance with test standards to be proposed in the Federal Register in July, 1981.

F. Reporting Requirements

For mammalian reproduction testing and subchronic cardiovascular testing, the EPA is proposing that a Study Plan be submitted 90 days before the initiation date of the test and preferably earlier than this deadline. Interim Quarterly Summary Reports are required for the reproductive toxicity test. Interim reports are required for subchronic cardiovascular toxicity at the end of each testing sequence. The proposed deadlines for submission of the Final Reports are 30 months from the date of the final test rule for reproduction testing and 23 months from the date of the final test rule for subchronic cardiovascular testing.

For all other testing proposed for dichloromethane, EPA is proposing that a Study Plan be submitted by the initiation date of the test and preferably earlier than this deadline. No interim reports are required. The proposed deadline for submission of the Final Report is 15 months for bird reproduction testing and the plant uptake/translocation test, and 12 months for all other tests. These deadlines are calculated from the effective date of the final rule. For a discussion of the basis for these frames, see the Federal Register of July 18, 1980 (45 FR 48535) and V. of this preamble.

G. Issues for Public Comment—Dichloromethane

1. What procedures will assure maintenance of the desired dose levels of dicholoromethane when administered in the diet for bird feeding studies?

The volatility of dichloromethane (b.p. 40°C) presents some difficulty in providing dosed diets for feeding studies, since the compound may be lost relatively rapidly by evaporation. EPA is proposing a requirement that the time be determined over which 25% loss of dichloromethane from the diet occurs, and that the replacement of treated diet be governed by this information. EPA is suggesting including the use of corn oil as a vehicle to reduce the likelihood of test substance loss. EPA is interested in comments as to the adequacy of these procedures and the availability of alternative procedures to assure that the desired dose levels are achieved.

2. Are the skin sentitization studies performed by Industrial Bio-Test adequate for dichloromethane?

Just before publication of this proposed test rule, Dow Chemical Company sent in two negative studies on the skin-sensitizing capacity of dichloromethane. Both were human studies one of 125 persons of all races, sexes, and a variety of ages. The other study was on 50 persons, also a mixed population. The studies were performed by Industrial Bio-Test on aerosol antiperspirant products. The products in the first test contained 20–21.5% dichloromethane, and were applied twice daily as a spray for 12 weeks. The other experiment used products containing 15% dichloromethane sprayed on patches which were applied for 24 hours, three times a week for three weeks, with a subsequent challenge two weeks later. The Agency invites comment on the use of these studies in fulfillment of the proposed skin-sensitization testing and requests that the following issues be addressed:

(a) the substances tested contained 15–21.5% dichloromethane. Although these compounds represent active products in use, the testing proposed by the EPA requires the use of a relatively pure chemical. Do the low concentrations compromise the value of the studies?

(b) Because the compounds tested were mixtures where dichloromethane was not the major component, there is a possibility that a negative interaction occurred, and that one or more other chemicals in the mixture masked or blocked a positive reaction to the dichloromethane. Is the likelihood of such an effect great enough to cause rejection of the studies' results?

(c) The EPA skin-sensitization test standard requires that a specific amount of chemical be injected intradermally to insure that exposure to a measured amount of the compound occurs. The human studies exposed the subjects in the manner by which they would normally be exposed to the particular products; directly by a spray, or indirectly, by spraying the substance and applying this to the skin. Using these methods the exact amounts applied cannot be determined. Are these drawbacks in methodology serious enough to invalidate the studies' results?

III. Nitrobenzene

A. Introduction

Nitrobenzene ($C_6H_5NO_2$; CAS No 98–95–3), also named nitrobenzol and oil of mirbane (Merck Index, 1976), is a pale yellow, oily liquid at room temperature and pressure with a characteristic bitter almond odor and a sweet taste.

The annual production of nitrobenzene was 575 million pounds in 1978. Nitrobenzene is manufactured by the direct nitration of benzene, using a mixture of nitric and sulfuric acids. Most of the crude product is converted to aniline. About 2.5–3 percent of the nitrobenzene produced each year, amounting to 12.75 million pounds, has various other uses, mostly as a solvent in the production of cellulose ethers and in Friedel-Crafts alkylation reactions, with one percent used (6 million pounds) in the manufacture of dye intermediates, metal polishes, and other solvent uses.

The Interagency Testing Committee recommended that nitrobenzene be tested for carcinogenicity, mutagenicity, and environmental effects.

B. Findings

1. *Health effects findings.* EPA is basing its proposed health effects testing requirement for nitrobenzene on the authority of section 4(a) (1) (A) of TSCA.

i. EPA believes that the manufacture, processing, distribution in commerce, use, and disposal of nitrobenzene may present an unreasonable risk of injury to human health due to reproductive and teratogenic activity, for the following reasons:

a. EPA has found that there are existing data and experience which indicate a potential human health hazard from nitrobenzene with respect to these effects.

b. EPA believes that persons are exposed to nitrobenzene in the workplace, as consumers, and as a result of release of nitrobenzene into the environment.

c. EPA does not believe that the rule will result in a loss to society of the benefits of the substance because the Agency's economic analysis has shown that the impact of test costs is minimal. (The Level I Economic Evaluation, available from the Industry Assistance Office, details the support for this belief.)

ii. Therefore, EPA believes that the activities in question may present an unreasonable risk. EPA also finds that there are insufficient data to predict the teratogenic and reproductive effects of nitrobenzene and that testing of nitrobenzene is necessary to develop such data. Therefore, EPA is proposing testing for structural teratogenic and reproductive effects. The proposed testing and reporting requirements for these effects are summarized in E. of this Preamble.

Health effects testing recommended by ITC or identified as an effect of concern but not proposed above, will be handled as follows:

a. Oncogenicity testing of nitrobenzene is being performed by the National Cancer Institute (NCI) and the EPA believes that NCI studies should be sufficient for the Agency's needs for oncegenicity, subchronic effects, and chronic effects testing; therefore, no additional testing for these effects is being proposed at this time.

b. EPA believes mutagenicity testing according to a testing sequence would be appropriate and will perform the initial tests itself because no criteria for progressing from initial testing to higher level tests are available. EPA will propose higher tier tests if needed based on analyses of lower tier results.

c. The EPA has decided not to proposed epidemiological testing at this

time because a suitable study population has not been identified.

d. Neurotoxicity/behavioral effects testing is not being required because EPA has not yet developed standards for these effects.

2. *Environmental effects findings.* EPA is basing its proposed environmental effects testing requirement on the authority of section 4(a) (1) (B) of TSCA.

i. EPA finds that nitrobenzene is produced in substantial quantities (575 million pounds in 1978).

ii. EPA also finds that there is substantial release to the environment. Of the nitrobenzene produced in the U.S. approximately 12.75 million pounds is expected to reach the atmosphere (1978 figures). A substantial quantity is believed to enter the equatic environment, and rainout would carry part of the atmospheric emission to soil and from there to water.

iii. EPA also finds with respect to the areas listed below, that there are insufficient data and experience to determine the effects resulting from the manufacture, processing, distribution in commerce, use, or disposal of nitrobenzene, and that testing is necessary to develop such data:

Aquatic Vertebrates
  Acute toxicity
  Chronic toxicity
Aquatic Invertibrates
  Chronic toxicity
Birds
  Acute toxicity
  Chronic toxicity
Terrestrial plants
  Root elongation/seed germination
  Early seedling growth
Bioconcentration
  Plant uptake/translocation
Chemical fate
  Soil adsorption

The proposed testing and reporting requirements for each of these effects are described in III.E. of this preamble.

EPA is not proposing testing on acute toxicity to aquatic invertebrates, aquatic plants, and mammals because data for these effects are sufficient. EPA will perform testing on some enviromental effects for which no standards are available as described in I.E. of this preamble.

The analysis and findings upon which the above determinations are based are presented in the Nitrobenzene Support Document which is available from the Industry Assistance Office.

C. Persons Required to Test

Section 4(b)(3)(B) specifies that the activities for which the Administrator makes section 4(a) findings (manufacture, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing, distribution, use, or disposal. Processors are required to test if the findings are based on processing, distribution, use, or disposal.

Because both health risk and exposure result from the manufacture, processing, and use of nitrobenzene, all persons who manufacture or intend to manufacture nitrobenzene, and who process or intend to process it within the period ending five years beyond the date required for the submission of the last Final Report will be subject to this test rule. Because "manufacture" is defined in section 3(7) of TSCA to include "import," importers of nitrobenzene are subject to this rule.

Every person subject to this rule does not have to individually conduct testing because TSCA contains provisions to avoid duplicative testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are required to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) specifically provides that any person required to test may apply to EPA for an exemption from that requirement.

EPA is not proposing to require the submission of equivalence data as a condition for exemptions from the proposed testing because EPA is requiring the testing of a technical grade of nitrobenzene that the Agency believes is representative of all grades currently being manufactured. Please see EPA's proposed statement of exemption policy for more information published in the Federal Register of July 18, 1980 (45 FR 48512).

D. Test Substance

The test substance will be nitrobenzene of at least 99.9 percent purity. This purity has been chosen because it is a widely-available representative technical grade and has been specified by the NCI for use in their testing.

E. Proposed Testing

The route of administration for health effects should correspond to the usual route of exposure to humans: inhalation. The route of administration for each environmental effects test is specified in the generic test standard for that effect with exceptions as noted below.

1. *Structural teratogenic effects.* EPA is proposing that a structural teratogenicity study be conducted in accordance with the structural teratogenicity test standard to be promulgated under 40 CFR 772.116-2. The proposed standard was published in the Federal Register of July 28, 1979 (44 FR 44054). Although the test standard allows for a choice of two species among four (hamster, rabbit, mouse, rat), the rat and a choice of one other species are proposed for this rule because the rat has been demonstrated to be sensitive to nitrobenzene in teratogenic tests.

2. *Reproductive effects.* EPA is proposing that a two-generation reproductive effects study of nitrobenzene in one rodent species be conducted in accordance with test standards to be promulgated under 40 CFR 772.116-3. The proposed standard was published in the Federal Register of July 28, 1979 (44 FR 44054).

3. *Aquatic vertebrates—acute toxicity.* The EPA is proposing acute toxicity testing on a coldwater species of freshwater fish in accordance with the test standards to be proposed in the Federal Register in July 1981. (See I.D. of this preamble for further discussion.) The static procedure is proposed because nitrobenzene degradation products are suspected of being a major factor in toxicity. The flow-through procedure would not allow degradation products to build up in the test vessel.

4. *Aquatic vertebrates—chronic toxicity.* The EPA is proposing early life stage toxicity testing on a coldwater and warmwater freshwater fish species and on a saltwater fish species in accordance with the test standards to be proposed in the Federal Register in July 1981. The coldwater freshwater species tested must be the rainbow trout (*Salmo gairdneri*) because this species is generally more sensitive to toxicants than the brook trout (*Salvelinus fontinalis*).

5. *Aquatic invertebrates—chronic toxicity.* The EPA is proposing life cycle toxicity testing on a freshwater and saltwater invertebrate in accordance with the test standards to be proposed in the Federal Register in July 1981. The freshwater invertebrate test must be static renewal because nitrobenzene degradation products are suspected of being a major factor in toxicity. The flow-through procedure would not allow degradation products to build up in the test vessel.

6. *Birds—acute toxicity.* The EPA is proposing acute toxicity testing on two species of birds in accordance with the proposed FIFRA guidelines published under 163.71-1 in the Federal Register of July 10, 1978 (43 FR 29696). The FIFRA guidelines for acute toxicity are being proposed as test standards specific to the chemicals in this rule. An acute oral

LD_{50} must be calculated or extrapolated to provide the basis for dose selection in a bird chronic toxicity test.

7. *Birds—chronic toxicity.* The EPA is proposing chronic toxicity testing on species of birds in accordance with the test standard to be proposed in the Federal Register in July 1981. Dose level selection must be as follows:

High dose ppm—0.125 x LD_{50} (in mg/kg) obtained in acute bird toxicity test.
Medium dose (ppm)—0.167 x high dose.
Low dose (ppm)—0.028 x high dose.

8. *Terrestrial plants—root elongation/seed germination.* The EPA is proposing root elongation/seed germination testing in accordance with the test standard to be proposed in the Federal Register in July 1981.

9. *Terrestrial plants—early seedling growth.* The EPA is proposing early seedling growth testing in accordance with the test standard to be proposed in the Federal Register in July 1981. Each species must be tested twice, once using the foliar route of exposure and once using the nutrient medium as the route of exposure, because plants may be exposed by either route.

10. *Bioconcentration—plant uptake/translocation.* The EPA is proposing plant uptake/translocation testing in accordance with the test standard to be proposed in the Federal Register in July 1981. The most sensitive monocot and the most sensitive dicot observed in the early seedling growth test must be tested because high sensitivity may be the result of high rates of uptake, and bioconcentration potential may differ significantly between monocots and dicots. Testing on more species is recommended but not required. Each species must be tested twice, once using the foliar route of exposure and once using the nutrient medium as the route of exposure, because plants may be exposed by either route.

11. *Soil adsorption.* EPA is proposing soil adsorption testing according to the test standard to be promulgated under 40 CFR 772.122-5. The proposed standard was published in the Federal Register of November 21, 1980 (45 FR 77352).

F. Reporting Requirements

Proposed reporting requirements for teratogenic effects are as follows. A Study Plan shall be submitted to EPA no later than the initiation of the teratogenic effects testing. No Interim Summary Reports will be required. The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

Proposed reporting requirements for reproductive effects are as follows. A Study Plan shall be submitted to EPA at least 90 days prior to the start of reproductive effects testing. Interim Quarterly Summary Reports shall be submitted to EPA beginning with the initiation of testing and ending with submission of the Final Report. The Final Report shall be submitted to EPA no later than 30 months after the effective date of this rule.

For all other testing proposed for nitrobenzene, EPA is proposing that a Study Plan be submitted by the initiation date of the test and preferably earlier. The deadline for submission of the Final Report is 15 months for bird reproduction testing and the plant uptake/translocation test, and 12 months for all other tests. These deadlines are calculated from the effective date of the final rule.

G. Major Issues for Comment

1. Should the Agency consider testing by dermal application?

In the health effects tests required, the route of administration is specified as inhalation. Nitrobenzene is rapidly absorbed through both the lungs and the skin. In studies of exposure of humans to vapor, more than twice as much was absorbed by inhalation as through the skin. It is suggested that dermal contact is a great hazard in industry and probably the most significant route of exposure for the general population, via products containing nitrobenzene as a solvent. Thus, there is reason to consider dermal application as the route of administration for testing. But since there is rapid absorption through the lungs, and the vapor pressure of nitribenzene is high, constant lung absorption is probable in any exposure situation, regardless of whether the worker makes skin contact with the liquid or vapor. It was this consideration that led EPA to propose inhalation as the route of administration.

IV. 1,1,1-TRICHLOROETHANE

A. Introduction

1,1,1-Trichloroethane, also known as methyl chloroform, is a colorless, nonflammable volatile liquid. Approximately 716 million pounds of 1,1,1-trichloroethane were produced in the United States in 1979, of which about 30 million pounds were exported. Imports of the chemical were essentially negligible. About 60 percent of the domestic production is obtained from vinyl chloride, about 30 percent is obtained from vinylidene chloride, and the remainder is produced by thermal chlorination of ethane.

Because 1,1,1-trichloroethane is an excellent solvent for greases, oils, tars, waxes and a wide range of other organic materials, its major use is in the metal cleaning industry, primarily in cold cleaning and vapor degreasing processes. An estimated 422 million pounds of 1,1,1-trichloroethane were consumed in these processes in 1979. It is also used in commercial and consumer products such as aerosols, adhesives, textiles, paints, inks, drain cleaners, film cleaners, spot removers, pharmaceuticals and leather tanners.

The Interagency Testing Committee (ITC) recommended that 1,1,1-trichloroethane be tested for carcinogenicity, mutagenicity, teratogenicity, and chronic effects (with specific attention to neurological, cardiovascular and renal systems) and that an epidemiology study be done.

B. Findings

The EPA is basing its proposed testing requirements on the authority of section 4(a)(1)(B) of TSCA.

EPA finds that 1,1,1-trichloroethane is produced in substantial quantities.

EPA also finds that substantial numbers of persons are exposed to 1,1,1-trichloroethane both in occupational settings involving manufacture, processing, and use of the chemical, and as consumers.

EPA also finds substantial release to the environment. Of the 1,1,1-trichloroethane produced in the United States in 1978, 75 percent was estimated to have been released into the environment. Measurable amounts of 1,1,1-trichloroethane have been reported in the atmosphere, soil, rainwater, marine and fresh surface waters, and groundwater. Residues of 1,1,1-trichloroethane have been measured in the tissues of aquatic and terrestrial plants and animals.

EPA also finds with respect to the following areas that there are insufficient data and experience to determine effects of the manufacture, processing, distribution in commerce, use, or disposal of 1,1,1-trichloroethane and that testing is necessary to develop such data:

Health Effects:
- Structural teratogenicity

Environmental Effects:

Aquatic vertebrates
- Acute toxicity
- Chronic toxicity

Aquatic invertebrates
- Chronic toxicity

Birds
- Chronic toxicity

Terrestrial plants
- Root elongation/seed germination
- Early seedling growth

Bioconcentration
- Plant uptake/translocation

The proposed testing and reporting requirements for each of these effects are described below.

Testing recommended by ITC or identified as an effect of concern but not proposed above, will be handled as described in the following paragraphs.

EPA is not proposing testing for acute health effects, reproductive effects, chemical fate or for certain environmental effects (acute toxicity to aquatic invertebrates, toxicity to mammals, acute bird toxicity, toxicity to algae, and aquatic vertebrate and invertebrate bioconcentration) because it believes that existing information is adequate. EPA will perform testing on some environmental effects for which no standards are available as described in I.E. of this preamble.

Oncogenicity testing of 1,1,1-trichloroethane is being performed by the National Cancer Institute (NCI) and the EPA believes that NCI studies should be sufficient for the Agency's needs; therefore, no oncogenicity testing is being proposed at this time.

EPA believes that mutagenicity testing according to a testing sequence would be appropriate, and will perform the initial testing itself because no criteria for progressing from initial test to higher level tests are available. EPA will propose higher tier tests if needed based on analysis of lower tier results.

The EPA has decided not to propose epidemiological testing at this time because a suitable study population has not been identified. No chronic effects testing is being proposed because the EPA is awaiting results of an ongoing NTP study which may provide sufficient data for the Agency's needs. The analysis and findings upon which the above determinations are based are presented in the 1,1,1-Trichloroethane Support Document which is available from the Industry Assistance Office.

C. Persons Required To Test

Section 4(b)(3)(B) specifies that the activities for which the Administrator makes section 4(a) findings (manufacture, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing, distribution, use, or disposal. Processors are required to test if the findings are based on processing, distribution, use, or disposal.

Because of the potential for exposure of industrial workers, consumers and the environment during the manufacture, processing, use and disposal of 1,1,1-trichloroethane, the EPA is proposing to require that persons who manufacture or process 1,1,1-trichloroethane and those who intend to manufacture or process 1,1,1-trichloroethane within the period ending five years beyond the date required for the submission of the last final report of this test rule, will be subject to this test rule. Because "manufacture" is defined in section 3(7) of TSCA to include "import," importers of trichloroethane are subject to this rule.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are required to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) specifically provides that any person required to test may apply to EPA for an exemption from that requirement.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing. As noted below, EPA is interested in evaluating the effects attributable to 1,1,1-trichloroethane itself, and is specifying a test substance to achieve this purpose. Please see EPA's proposed statement of exemption policy for more information published in the Federal Register of July 18, 1980 (45 FR 48512).

D. Test Substance

All commercial grades of 1,1,1-trichloroethane contain up to 8 percent stabilizer(s). Although several hundred additives have been patented, most are not used regularly. Some of those which have been identified in the various commercial products and the percent by volume of the product are: nitromethane, 0.4–1.8 percent; butylene oxide, 0.4–0.8 percent; dioxane, 2.5–3.5 percent; dioxolane, 1.0–1.4 percent; methyl ethyl ketone, 1.0–1.4 percent; toluene, 1.0–1.4 percent; sec-butyl alcohol, 0.2–0.3 percent; and isobutyl alcohol, 1.0–1.4 percent. The potential toxicological effects of some of these stabilizers may make it difficult to evaluate 1,1,1-trichloromethane's toxicity from tests on a technical grade substance. Unstabilized 1,1,1-trichloroethane is available in small quantities at high cost; however, it is not known how long it remains pure once exposed to air. Therefore, EPA is proposing a 1,1,1-trichloroethane test substance containing 0.5 percent butylene oxide stabilizer for use in tests proposed in this rule for 1,1,1-trichloroethane. This product contains the least amount of stabilizer of any product available and is currently being used by NTP in an oncogenicity bioassay on 1,1,1-trichloroethane.

E. Proposed Testing

Because the most extensive human exposure is through inhalation, the proposed route of administration for the health effects testing is inhalation.

The route of administration for each environmental effects test is specified in the generic test standard for that test with exceptions as noted below.

The following are effects of concern discussed in I.C. of this preamble for which EPA is proposing testing.

1. *Teratogenicity.* The EPA is proposing that a structural teratogenicity study be conducted in accordance with the structural teratogenicity standards to be promulgated under 40 CFR 772.116–2. The proposed standard was published in the Federal Register of July 26, 1979 (44 FR 44054).

2. *Aquatic vertebrates—acute toxicity test.* The EPA is proposing acute toxicity testing on a coldwater species of freshwater fish in accordance with test standards to be proposed in the Federal Register in July 1981. The flow-through procedure is necessary because 1,1,1-trichloroethane is highly volatile. Evaporation of 1,1,1-trichloroethane in the static procedure would result in difficulty in maintaining nominal exposure levels.

3. *Aquatic vertebrates—chronic toxicity.* The EPA is proposing early life stage toxicity testing on a coldwater and warmwater freshwater fish species and on a coldwater saltwater fish species in accordance with test standards to be proposed in the Federal Register in July 1981. The coldwater freshwater species tested must be the rainbow trout (*Salmo gairdneri*) because this species is generally more sensitive to toxicants than the brook tyrout (*Salvelinus fontinalis*).

4. *Aquatic invertebrates—chronic toxicity.* The EPA is proposing life cycle toxicity testing on a freshwater and saltwater invertebrate in accordance with test standards to be proposed in the Federal Register in July 1981. The freshwater invertebrate test must be flow-through, or static with precautions taken to avoid loss of test substance due to the volatility of 1,1,1-trichloroethane. Evaporation of 1,1,1-trichloroethane in the static renewal procedure may result in difficulty in maintaining nominal exposure levels.

5. *Birds—chronic toxicity.* The EPA is proposing chronic toxicity testing in two species of birds in accordance with the test standard to be proposed in the Federal Register in July 1981. Does level

selection is proposed to be made as follows:

High dose (ppm)—2510 mg/kg x0.125
Medium dose (ppm)—0.167 X high dose
Low dose (ppm)—0.023 X high dose

Also, because 1,1,1-trichloroethane is highly volatile, special dietary procedures are proposed.

6. *Terrestrial plants—root elongation/seed germination.* The EPA is proposing root elongation/seed germination testing in accordance with the test standard to be proposed in the Federal Register in July 1981.

7. *Terrestrial plants—early seedling growth.* The EPA is proposing early seedling growth testing in accordance with the test standard to be proposed in the Federal Register in July 1981. Each species must be tested twice, once using the foliar route of exposure and once using the nutrient medium as the route of exposure, because plants may be exposed by either route and toxicity may significantly depend upon the route of exposure.

8. *Bioconcentration—plant uptake/translocation.* The EPA is proposing plant uptake/translocation testing in accordance with the test standard to be proposed in the Federal Register in July 1981. The most sensitive monocot and the most sensitive dicot observed in the early seedling growth test must be tested because high sensitivity may be the result of high rates of uptake, and bioconcentration potential may differ significantly between monocots and dicots. Testing on more species is recommended but not required. Each species must be tested twice, once using the foliar route of exposure and once using the nutrient medium as the route of exposure, because plants may be exposed by either route.

F. Reporting Requirements

For all testing propose for 1,1,1-trichloroethane, EPA is proposing that a Study Plan be submitted by the initiation date of the test and preferably earlier than this deadline. No interim reports are required. The proposed deadline for submission of the Final Report is 15 months for bird-reproductive testing and the plant uptake/translocation test, and 12 months for all other tests. These deadlines are calculated from the effective date of the final rule. For a discussion of the basis of these time frames, see FR 48535 (July 18, 1980) and V. of this preamble.

G. Major Issues for Public Comment

1. Which product should be used for testing?

See III.D. of this preamble for discussion.

2. What procedures will assume maintenance of the desired dose levels of 1,1,1-trichloroethane when administered in the diet for bird feeding studies?

The volatility of 1,1,1-trichloroethane (vapor pressure-100 mm at 20°C) presents some difficulty in providing dosed diets for feeding studies since the compound may be lost relatively rapidly by evaporation. EPA is proposing a requirement that the time be determined over which 25 percent loss of 1,1,1-trichloroethane from the diet occurs, and that the replacement of treated diets be governed by this information. EPA is suggesting the use of corn oil as a vehicle to reduce the likelihood of test substance loss. EPA is interested in comments as to the adequacy of these procedures and the availability of alternative procedures to assume that the desired dose levels are achieved.

3. Should teratology testing be proposed?

The York et al. teratology study failed to demonstrate any maternal toxicity. Such toxicity is generally regarded as a mandatory element of any teratology test from which a reasonable determination of lack of teratogenic effects can be made. Nevertheless, this study was conducted at a level that was seven times the TLV. While it appears clear that this study would not be sufficient to reasonably determine that no unreasonable risk of teratogenicity exists, is the data sufficient to reasonably predict that no unreasonable risk of terata exists?

V. Reporting Requirements

A. Study Plans and Interim Quarterly Summary Reports

In the first proposed section 4 test rule published in the Federal Register of July 18, 1980 (45 FR 48510), EPA proposed requiring Study Plans for all tests required under any section 4 test rule and also Interim Quarterly Summary Reports for all long-term tests. EPA also proposed in the first rule that long-term test Study Plans must be submitted 90 days before initiation of the test, while short-term test Study Plans only need to be submitted by the date of test initiation. The rationale behind these proposed requirements was provided in the first test rule and will therefore not be repeated here. An analysis of the comments received on these proposed requirements will be provided in the preamble to the final rule based on the July 18, 1980 proposal which should be promulgated in the fall of 1981. Any changes made as a result of those comments will be reflected in the final rule for dichloromethane, nitrobenzene, and 1,1,1-trichloroethane.

Interim reporting requirements are proposed for cardiovascular testing because it is a lengthy test. Interim reports would provide a current status of the study. These reports should be brief and impose minimal burden, but would provide summary information on such things as hemodynamic parameters, statistics on the hemodynamic parameters, histopathological changes in tissues examined, and biochemical parameters. Because dosing is proposed to be performed sequentially, EPA is proposing that the reports be submitted at the end of each testing sequence rather than on a quarterly basis.

Reporting requirements for reproductive effects were discussed in the July 18, 1980 proposal (45 FR 48510). Because of the length of the test, submission of a Study Plan at least 90 days prior to the start of testing and submission of Interim Quarterly Summary Reports were proposed.

All remaining tests proposed in this rule (i.e., dermal sensitization testing and all environmental effects and fate testing) are short-term tests; therefore, Study Plan deadlines are the date of test initiation and no Interim Quarterly Summary Reports are required.

B. Final Report Deadline

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. In determining deadlines for submission of Final Reports for each type of test, EPA has considered and allowed an amount of time it believes is reasonable for a number of factors that affect the time period needed for satisfactory testing. These factors include coordination among persons subject to the rule to permit agreement on joint testing programs, development of Study Plans, set-up and execution of required tests, analysis of test results, and preparation of Final Reports. The proposed time frame for these factors as they relate to tests proposed in this rule on structural teratogenicity, reproduction, and subchronic effects are detailed in the first proposed section 4 test rule published in the Federal Register of July 18, 1980 (45 FR 48510). An analysis of comments received on the first proposed rule will be provided in the preamble to the final rule based on the July 18, 1980 proposal which should be promulgated in the fall of 1981.

Using the same approach as was used in the July 18, 1980, proposal, the

proposed Final Report deadline for subchronic cardiovascular testing (23 months after the effective date of this rule) has been determined in Table 1 by adding the time estimated to accomplish each of the tasks listed above.

Table 1.—*Time frame for subchronic cardiovascular testing (months)*

Activities	Allotted times
1. Coordination among test sponsors	2
2. Study plan preparation [1]	4
3. 90-day pre-test reporting requirement	3
4. Test performance [2]	9
5. Analysis of test results, preparation of final report	5
6. Final report deadline	23

[1] Study Plan preparation: The time period allotted for Study Plan preparation is indicated below and is designed to permit the necessary activities precedent to initiation of the required testing.

[2] Time periods reflect time to perform three tests in accordance with the maximum number of repetitions in EPA's test rule.

Study Plan Time Frame (months)

Activities	Time allotted
1. Acquisition and acclimation of test animals	1
2. Development of experimental protocol	1
3. Control catheterization for each dog following exposure to air for one week in inhalation chamber	1
4. Determination of epinephrine doses in each dog for the cardiac sensitization portion of the protocol	1
Total	4

For all other tests EPA proposes that a Final Report deadline of 12 months from the effective date of the Final Rule is reasonable with the exception of the bird reproduction test and the plant uptake/translocation test, which are allowed 15 months each. These proposals are based on the fact that each test, except bird reproduction and plant uptake/translocation, has a comparable or shorter test performance time period than the 90-day subchronic health effects test for which a Final Report deadline of 12 months was proposed in the first rule. When the other activities, (i.e., coordination among test sponsors, Study Plan preparation, data analysis, and Final Report preparation), were considered collectively, the time period for each test was determined to be comparable or shorter than the 90-day subchronic health test. The Final Report deadline for the bird reproduction test includes an additional three months because the test performance period lasts 5–6 months. The Final Repart deadline for the plant uptake/translocation test also includes an additional three months because the test performance period lasts 4–6 months.

VI. General Issues for Public Comment

The public is encouraged to submit comments on various matters discussed in the preamble and accompanying support documents In addition, EPA specifically requests comments on the issues relating to specific chemicals highlighted at the end of each chemical specific section and the general issues discussed below.

1. Should section 4(a)(1)(B) findings be made on a case-by-base basis or should criteria be developed for substantial production/release and exposure? If so, what criteria should be recommended?

EPA has chosen to make section 4(a)(1)(B) findings on a case-by-case basis in this rule rather than define criteria for substantial production, substantial release and substantial or significant human exposure. The Agency believes that it does not have the experience at this time to establish such criteria. If specific criteria are desirable for future test rules, EPA would appreciate specific recommendations and why they are appropriate.

2. Are the effects of concern identified by EPA appropriate for the chemicals in this rulemaking?

In I.C. of this preamble EPA identified certain health effects for dichloromethane and 1,1,1-trichloroethane and environmental effects for all three chemicals contained in this rule on the basis of exposure characteristics for the purposes of determining the adequacy of information under a section 4(a)(1)(B) finding. The Agency seeks comment on whether there are available data or exposure to reasonably determine or predict the effects of chemicals in some or all of the identified areas of concern or if additional areas of testing should be considered by EPA.

3. Are the reporting deadlines proposed in today's rule appropriate?

This rule proposes reporting requirements for the subchronic cardiovascular test, dermal sensitization test, and various environmental effects (see V. of this preamble). Reporting deadlines for other health effects were proposed in the Federal Register of July 18, 1980 (45 FR 48535).

VI. Economic Analysis of Proposed Rule

To evaluate the potential economic impact of test rules, EPA has adopted a 2-stage approach. All candidates for test rules go through a Level I analysis; this analysis consists of evaluating each chemical (or chemical group) on four principal market characteristics: (1) demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The results of the Level I analysis (along with consideration of the cost of the required tests) indicate whether the possibility of a significant adverse economic impact exists. Where the indication is negative, no further economic analysis is done for that chemical substance or group. However, for those chemical substances or groups where the Level I analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted. This Level II analysis attempts to predict more precisely the magnitude of the expected impact.

Cost of the Test Requirements for Nitrobenzene, Dichloromethane, and 1,1,1-Trichloroethane

[Dollars in thousands]

Compound	Total cost	Annualized cost [1]
Nitrobenzene	$224–708	$58.1–183.4
Dichloromethane	236–744	61.3–192.8
1,1,1-Trichloroethane	86–292	22.4–75.8

[1] 25 percent cost of capital for 15 years.

A. Dichloromethane

The Level I analysis indicated that no significant economic impact to dichloromethane producers would result from the proposed test rule. A Level II analysis was unnecessary.

This conclusion is based on the following considerations: first, the demand for dichloromethane in its major markets appears to be relatively insensitive to changes in price. Furthermore, the market outlook for dichloromethane is quite optimistic. In addition, the per unit cost increase attributable to testing is very small, up to 0.03 cents per lb., or 0.15 percent of the 1979 price (based on 1979 production of 633.2 million lbs.). Such small cost increases could probably be passed on by producers and none of the producers should be particularly impacted by the increased cost.

B. Nitrobenzene

The Level I analysis indicated that the proposed test rule will not pose any significant economic impact on nitrobenzene manufacturers. A Level II analysis was not needed.

This conclusion is based upon the following considerations: first, the demand for nitrobenzene (and products derived from nitrobenzene) appears to be expanding and market prospects for this compound seem quite good. Second, a small number of large firms produce nitrobenzene, and no firm is expected to be placed at a comparative disadvantage due to testing costs. In addition, the per unit cost increase due

to testing is extremely small, about .01 to .02 cents per pound or .03 percent to .08 percent of the 1979 price (based on 1979 production of 952.4 million lbs.).

C. 1,1,1-Trichloroethane

Again, the Level I analysis indicated that the proposed test rule will not pose any significant economic impact on 1,1,1-trichloroethane producers. A Level II analysis was not needed.

The following factors contributed to this conclusion: first, the demand for 1,1,1-trichloroethane is expected to grow modestly but steadily. Second, the firms producing 1,1,1-trichloroethane all have a significant share of the market and none are expected to be at a comparative disadvantage in absorbing costs. Finally, the per unit cost increase due to testing is extremely small, ranging up to .01 cent per pound or 0.07 percent of the 1979 price (based on 1979 production of 716.3 million lbs.).

VIII. Availability of Test Facilities and Personnel

In addition to the requirements discussed previously, section 4(b)(1) requires EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing proposed in this rule." The Agency believes that there will be available resources to perform the required testing. EPA today proposes testing for three single chemicals only and anticipates that many manufacturers and processors subject to the rule will elect to arrange for joint testing or apply for an exemption from testing to minimize the number of tests that will be performed. Furthermore, this is only the second test rule proposed by EPA; therefore, the cumulative impact of EPA actions would be expected to be small. Because this may not be the case after EPA promulgates several test rules, EPA has initiated a study of the availability of test facilities for future section 4 test rules.

IX. Environmental Impact Statement

EPA is not required to prepare environmental impact statements under the National Environmental Policy Act (NEPA), 41 U.S.C. 4321 et seq. for test rules, and has determined that voluntary preparation of an environmental impact statement is not appropriate for regulations issued under section 4 of TSCA. See the preamble to the Agency's rules for compliance with NEPA published in the Federal Register of November 6, 1979 (44 FR 64174).

X. Public Meetings

If persons wish to present comments and questions on these proposed rules to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting on September 17, 1981 in Washington, D.C. An opportunity for presentation of oral comments is required by section 4(b)(5). This meeting is scheduled after the deadline for submission of written comments on the proposed rule to allow EPA and the public commentors to discuss issues raised in written comments. Information on the exact time and place of the meeting is available from the Industry Assistance Office.

Persons who wish to attend or present comments at the meeting should call the OTS Industry Assistance Office toll-free number 800–424–9065 (in Washington, D.C., 554–1404). While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and designated EPA participants. Persons who wish to attend the meeting should call the Industry Assistance Office before making travel plans since the meeting will not be held if members of the public do not wish to make oral comments.

The Agency will transcribe each meeting and will include the written transcripts in the public record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will become part of EPA's record for this rulemaking.

XI. Public Record

EPA has established a public record for this rulemaking (docket number OPTS–47004) which is available for inspection in the OPTS Reading Room from 8:00 a.m. to 4:00 p.m. on working days (Rm. E–107, 401 M St., SW., Washington, D.C. 20460). This record includes basic information considered by the Agency in developing this proposal. The Agency will supplement the record with additional information as it is received. The record includes the following information:

(1) Federal Register notices pertaining to this rule:

(a) Notice of proposed rule on nitrobenzene, dichloromethane and 1,1,1-trichloroethane.

(b) Notices containing the ITC designation of nitrobenzene, dichloromethane and 1,1,1-trichloroethane to the Priority List.

(c) Notices containing EPA's proposed health effects test standards and Good Laboratory Practice Standards (44 FR 27334 and 44 FR 44054).

(d) Notice of proposed rule on exemption policy and procedures.

(e) Notice containing the Notice of Proposed rule on reimbursement policy and procedures.

(f) Notice containing EPA's proposed environmental effects test standards.

(g) Notice containing EPA's proposed chemical fate test standards.

(h) Notice of proposed rulemaking on chloromethane and chlorinated benzenes (45 FR 48524).

(2) Support documents:

(a) Dichloromethane Support Document.

(b) 1,1,1-Trichloroethane Support Document.

(c) Nitrobenzene Support Document.

(d) Level I Economic Evaluation: Dichloromethane.

(e) Level I Economic Evaluation: 1,1,1-Trichloroethane.

(f) Level I Economic Evaluation: Nitrobenzene.

(3) Minutes of Informal Public Participation Meetings.

(4) Communications Before Proposal:

(a) Written: Public and Intra-agency or Interagency Memoranda and Comments.

(b) Memoranda of telephone conversations.

(c) Meetings.

(5) Public comments on the ITC reports.

(6) Reports—published and unpublished data.

XI. Classification of Rule

Under Executive Order 12291, EPA must judge whether a regulation is "Major" and therefore subject to the requirement of a Regulatory Impact Analysis. The regulations for these three chemical substances are not major because they do not meet any of the criteria set forth in section 1(b) of the Order. First, the annual cost of the testing prescribed for the three chemicals is less than $1 million over the testing and reimbursement period. (Nitrobenzene: $58,000–182,000; 1,1,1-Trichloroethane: $60,000–188,000; dichloromethane: $84,000–261,000.) Second, because the cost of the required testing will be distributed over very large quantities of production, the rules will have only very minor effects (less than 0.1 percent a year) on producer's cost or user's prices for each of the chemicals. Finally, taking into account the nature of the market for these products, the low level of costs involved, and the expected nature of the mechanisms for sharing the costs of the required testing, EPA concludes that there will be no significant adverse economic effects of any type as a result of this rule.

The regulation was submitted to the Office of Management and Budget for

review as required by Executive Order 12291. Any comments from OMB to EPA, and any EPA response to those comments, are included in the public record.

XIII. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (RFA), (15 USC 601, Pub. L. 96-354, Sept. 19, 1980), EPA is certifying that these testing rules, if promulgated, will not have a significant impact on a substantial number of small entities.

The test rules, if promulgated, may impose some costs on manufacturers, processors and users of the chemicals. Manufacturers (which, for the purposes of this rule includes importers) and processors of the chemicals will be subject to a requirement to either perform the required testing, or obtain an exemption based on the fact that the testing will be carried out by another person. Although EPA has not adopted a definition of small business for TSCA section 4 purposes, EPA's economic analysis has identified the manufacturers and importers of the three chemicals and none of these firms could be considered a small business by any reasonable definition. All have total sales in excess of $100 million.

The Agency has not attempted to identify the large number of companies which would be subject to these testing rules as "processors." However, even assuming that a large number of these processors are small businesses, EPA has several bases for concluding that none will experience a significant economic impact as a direct result of these rules.

1. Small processors will not perform testing themselves, or to participate in organization of the testing effort. Based on comments from industry, EPA expects that, after this rule becomes final, manufacturers of the substance (and perhaps major processors) will attempt to organize a testing consortium to pay for the required testing. After a suitable period, one or more parties are expected to indicate to EPA that they will take responsibility for developing the required data. Because there are many large companies involved with each of these chemicals, both as manufacturers and processors, there is no reason to anticipate that any small business will be involved in these discussions.

2. Small processors will experience only very minor costs in securing exemption from testing requirements. Once these testing responsibilities are accepted, persons not included in the testing consortium (including any small business) would be required to obtain an exemption from testing [TSCA section 4(c)]. EPA believes that the cost of applying for an exemption would be very small. Under the proposed exemption policy published in the Federal Register of July 18, 1980 (45 FR 58512) the application would need to identify the applicant, the requirements from which the applicant was seeking an exemption, and citation of the study or studies upon which the exemption may be based. These minimal requirements may be reduced even further in light of comments on the proposed exemption policy.

3. Small processors are unlikely to be affected by reimbursement requirements. Any person who receives an exemption would be subject to a statutory requirement [TSCA section 4(c)(3)] to provide a "fair and equitable reimbursement" to the person or persons who assumed prime responsibility for testing. However, EPA believes that the legal liability of small processors to provide reimbursement is likely to remain a theoretical one, because existing voluntary testing groups often waive reimbursement from many small manufacturers and most processors. Therefore such processors will not be directly affected by the need to provide reimbursement or by the administrative costs of participation in the reimbursement process. EPA's proposed reimbursement rules presume that only manufacturers will contribute directly, although they leave open the possibility that manufacturers will seek contributions from some or all processors in particular situations. If reimbursement is sought from processors, the extent of the burden to be imposed on small businesses will depend on EPA's reimbursement procedures, including reporting requirements for processors and the formula for allocating testing costs between processors and manufacturers, and among processors. However, even in these cases the impact on processors would be softened by the TSCA requirement that market share and competitive position be considered in determining reimbursement. A more detailed discussion of the impact of these features on small businesses will be found in EPA's forthcoming proposed rule for section 4 reimbursement.

Processors of the chemicals which are not subject to reimbursement requirements, and users of the chemicals, may experience an indirect impact as a result of cost increases imposed on manufacturers and other persons who either pay for the testing initially or provide reimbursement to those who do. However, even if the entire per-pound cost is passed on through the market, EPA's Economic Evaluation shows that there would be no significant impact. The estimated percentage cost increase which may result from these rules is a fraction of one percent per chemical.

XIV. Paperwork Reduction Act

The Paperwork Reduction Act of 1980 (PRA) (44 U.S.C. 3501 *et seq.*) authorizes the Director of the Office of Management and Budget to review certain information collection requests by federal agencies. The test rules proposed in this notice, if promulgated, could result in the submission of several types of information related to the required testing, including study plans for each test required, interim reports on the status of certain tests as they are being conducted, and final reports for all tests by various manufacturers and processors subject to the testing requirement. For the reasons set out below, however, EPA believes that the test rules contained in this notice do not constitute information collection requests as defined in the PRA.

On the basis of industry comments, EPA believes that in most cases a single consortium or person would step forward to perform all the tests or one particular test for a chemical. If one or more persons accept responsibility for the conduct of testing, under section 4(c) of TSCA other manufacturers and processors of the chemical may be relieved from performance of testing by application to the Administrator although they might bear some responsibility for the costs of testing. Thus the requirements for submittal of a study plan, interim reports, and a final report for required tests do not appear to constitute an "information collection request" under sections 3502(4) and (11) of PRA, because they would not impose identical reporting requirements on ten or more persons. Even if several persons take responsibility for testing, the reporting called for by these rules consists of information which is uniquely related to the different tests which are being required.

EPA's rules for submittal of exemption applications under section 4(c) of TSCA were proposed on July 18, 1980 (45 FR 48512). Section 770.405 and .406 of EPA's proposed rules set forth the requirements for filing and content of exemption applications. Because these rules were proposed before the effective date of the PRA, they were not subject to that portion of the Act which requires that proposed rules containing a collection of information requirement be submitted to the Director of OMB. Nevertheless, the actual exemption

application process is triggered by the promulgation of test rules on particular chemicals. In view of this, it is possible that proposal of particular test rules may be viewed as the appropriate time for OMB review of the information collection aspects of exemption applications. However, EPA believes a generic treatment of the applicability of the requirements of the PRA to exemptions is more appropriate. EPA takes this position because the Agency is considering suggestions for modification of the exemption reporting requirement contained in the July proposal which, if accepted, would minimize the significance of this issue. Comments received on that proposal suggested that in certain circumstances exemptions be granted automatically, without the requirement for an application. Because the issues relating to exemption applications were fully addressed in that earlier rulemaking, EPA is not requesting comment on the subject in this notice.

Imposition of testing requirements could eventually trigger a requirement to report certain information in connection with a reimbursement proceeding. Comments from interested industries cause EPA to believe that this will happen only rarely. EPA's proposed reporting requirements in connection with reimbursement proceedings will be addressed in a forthcoming notice.

Although this proposed rule does not contain any information collection requirement subject to the review and clearance functions of the PRA, in the course of reviewing these testing rules and associated requirements such as exemption rules, EPA will give full consideration to whether the information sought is necessary and will have practical utility to the Government. In addition, if a determination is later made that any of these requirements are subject to the PRA, EPA will ensure that any information collection contained in the final rule fully complies with the applicable procedural requirements.

Dated: May 29, 1981.

Anne M. Gorsuch,

Administrator.

Therefore, it is proposed that Chapter I of 40 CFR Subpart B be amended by adding §§ 773.1500, 773.3050 and 773.4400 to proposed Part 773 to read as follows:

Subpart B—Chemical Substances

§ 773.1500 Dichloromethane.

(a) *Identification of test substance.* (1) Dichloromethane (CAS 75–09–2, also know as methylene chloride) shall be tested in accordance with this Part.

(2) Dichloromethane of 99.95% purity or greater and specific gravity of 1.320, shall be used as the test substance in all tests. The test substance shall contain no stabilizers.

(b) *Persons required to test.* (1) All persons who manufacture, process, or intend to manufacture or process dichloromethane from (effective date of this rule) to (five years form the date the last final report is due) shall conduct tests and submit data as specified by this Part.

(2) Any person subject to the requirements of this section may apply to EPA for an exemption from testing pursuant to Subpart E of Part 770.

(c) *Health effects testing*—(1) *Acute effects-dermal sensitization*—(i) *Required testing.* (A) An acute dermal sensitization study shall be conducted on dichloromethane in accordance with the test standard in 772.112–26 of this chapter.

(B) The route of administration shall be intradermal injection. Appropriate dilution must be done if excessive irritation or ballooning of tissue occurs using neat dichloromethane.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

(2) *Subchronic cardiovascular toxicity*—(i) *Study design.* (A) *Species and age.* Testing must be performed on young adult dogs.

(B) *Number and sex of animals.* At least three dogs must survive the test period. Dogs of the same sex are required.

(C) *Exposure concentration level.* The dogs will be exposed initially to 250 ppm dichloromethane in an inhalation chamber. However, if repetition of the study is required based on a determination described in paragraph (c)(2)(iii) of this section, each repetition shall use one-half the previous exposure concentration.

(D) *Duration of testing.* Animals must be exposed to dichloromethane at least 7 hours per day, 5 days per week over a 90-day period.

(E) *Controls.* Each dog shall serve as its own control.

(ii) *Study conduct.* Standards for the performance of a subchronic inhalation study can be obtained in § 772.112–33 of this chapter. General laboratory practice standards for health effects testing published in section 772.100–2 of this chapter must be followed.

(A) *General.* Each dog must be challenged with epinephrine hydrochloride prior to the exposure to dichloromethane and once a month thereafter during the 90 day test period. This experiment must be carried out prior to the cardiac catheterization (or equivalent technique for hemodynamic measurements) since it is important that stress to the animal be minimized during this procedure. The epinephrine should be administered intravenously and only electrocardiographic (EKG) monitoring is required. Prior to dichloromethane exposure, each dog shall be challenged with increasing doses of epinephrine to establish a minimum effective dose which would give rise to ectopic beats or more serious arrythmias in the individual animals. EKG changes must be recorded during each drug challenge. This procedure shall be repeated at 1, 2 and 3 month intervals during exposure to dichloromethane. When determining the new minimum effective dose at each 30-day time period, the starting dose for epinephrine in the series of challenges shall be 1/5 of the previously established minimum effective dose. Increased doses of epinephrine should be administered at 30 minute intervals until a new minimum effective dose is established.

(B) *Observations.* Animals must be under surveillance for any overt physiological and behavioral changes during inhalation exposure.

(C) *Catherterization.* (*1*) The procedure to be used for the cardiotoxicity testing of dichloromethane is right and left heart catheterization in the unanesthetized dog. Guidance for the methodology can be obtained by modification of the procedure of Will and Bisgard (1972). Cardiac catheterization of unanesthetized large domestic animals. (Journal of Applied Physiology. 33: 400–401). However, other established techniques using the unanesthetized dog are acceptable provided that the technique allows for the accurate measurement of the designated hemodynamic parameters. Several techniques are documented in the literature which utilize indwelling monitoring devices such as catheters and pressure transducers. These procedures may lead to difficulty in maintaining animal survival for the specified treatment period. However, if a procedure is employed using indwelling monitoring devices, a non-halogenated anesthetic which has no cardiac activity shall be used to carry out the surgical implantation of such devices. In addition, an adequate postoperative period shall be allowed for recovery from the anesthesia since all hemodynamic measurements must be

determined on the unanesthetized animal.

(2) A control cardiac catheterization shall be performed on each animal following a one week exposure to circulating air in an inhalation chamber for seven hours per day, five days per week. Following the control period, each dog shall be exposed in an inhalation chamber to an atmospheric concentration of 250 ppm dichloromethane. At the end of each 30 day interval, a left and a right heart catheterization shall be performed on each animal. If a technique is employed which necessitates a catheterization prior to each data collection, a minimum of a one hour equilibration period is required between the completion of catheterization and the initiation of data collection. In the event that indwelling devices are used in the study, a minimum of one hour equilibration period is also required for each dog after it has been secured to the monitoring instrument(s).

(D) *Cardiovascular testing.* (1) The parameters which are to be measured in each animal during the control catheterization and the catheterization performed at 30 day intervals during exposure are as follows: atrial and pulmonary capillary wedge pressures; ventricular pressures; aortic and pulmonary artery pressures; blood O_2 saturations; the calculation of cardiac output (e.g., using the Fick Principle or the Indicator Dilution Method) and vascular resistance; the rate of rise of left ventricular pressure with time (LV dP/dt); electrocardiogram—Standard Lead II; heart rate; and determination of dichloromethane content in the blood.

(2) A control carboxyhemoglobin measurement must be made followed by a measurement at two and four weeks after the start of exposure to dichloromethane. If the two and four week measurements do not differ statistically from the control measurement of each dog, carboxyhemoglobin measurements may be performed at one month intervals, thereafter. However, if the carboxyhemoglobin levels recorded at the second and fourth weeks are statistically different from the control measurements, carboxyhemoglobin analysis should then be performed at two week intervals until the termination of exposure. Procedures and literature references for carboxyhemoglobin analysis of the blood can be obtained by references to Curtius and Roth (1978. Clinical biochemistry: principles and methods, Vol. II Berlin/New York: Walter de Gruyter and Co.).

(E) *Body weights.* Animals must be weighed at least weekly. At the end of the 90-day experimental period the dogs will be sacrificed for pathological examination.

(F) *Handling of moribund and dead animals.* All moribund animals must be sacrificed and undergo gross necropsy; the designated tissues must be taken for histopathology. Those animals found dead during the course of the study must undergo gross necropsy and the tissues designated for histopathology must be salvaged if death occurred within 16 hours of necropsy.

(G) *Pathology procedure*—(1) *Gross necropsy.* The gross necropsy shall include an initial physical examination of the external surfaces and all orifices followed by an internal examination of tissue and organs in situ. Speical examination shall be made and reported concerning th stutus of the pericardial sac, any abnormalties of the pericardial fluid, epicardial surface, coronary arteries, myocardium, endocardium, atria septa, valves, chordac tendinae, and papillary muscles. The thickness of the myocardium of the right and left ventricles shall be measured and recorded. In addition, a detailed gross examination shall be made of any gross lesions, the lungs, kidneys, liver adrenals and aorta.

The weight of the heart, lungs, liver, and kidneys shall be recorded after careful dissection and trimming.

(2) *Histopathology examinations.* Histopathological examinations are required only when a significant change is observed in one or more of the following parameters after 90 days of exposure: the minimum effective dose of epinephrine which produced ectopic beats and/or more serious arrythmias, electrocardiogram carboxyhemoglobin levels in the blood, cardiac output, LV dp/dt, and ventricular pressures. Following tissue fixation in an appropriate fixative for the specific tissue(s), the following microscopic examination shall be made: all gross lesions (with a margin of normal tissue); heart (representative sections of the atrium, right and left ventricles, including SA and AV nodal tissue, and cross sections of the right and left coronary arteries); lungs (representative sections from each lobe(s)); liver (two lobes); kidneys (representative sections from both kidneys to include cortex, medulla, and renal pelvis); aorta (representative section from abdominal aorta at iliac bifurcation and arch of aorta at the origin the brachcocephalic branches, left common carotid, and left subclavian arteries.

(iii) *Data evaluation.* Statistical analysis on all measured hemodynamic parameters should be carried out using an analysis appropriate to the repeated measures design of the study. Examples of such analysis include analysis of variance (or Friedman's ranked sums) and profile analysis; however, the multiple paired t-test on control versus dosed time periods or pairwise Hotelling's T^2 using all parameters simultaneously will be considered acceptable. If, at the end of the 90 day experimental period, exposure to 250 ppm dichloromethane does not result in statistically significant alterations from control in the electrocardiogram and one of the following parameters: ventricular pressure, cardiac output and vascular resistance, or LV dP/dt, then no additional testing need be done. Measurement of these parameters is required by paragraph (c)(3)(ii)(D)(1). On the other hand, if exposure to dichloromethane *does cause* statistically significant alterations from control in the electrocardiogram and one of the following parameters: venticular pressure, cardiac output and vascular resistnace, or LV dP/dt, then the 90 day subchronic study must be repeated two additional times unless a no observable effect level is reached on the first repetition. Each repetition of the study shall use one-half the previous exposure concentration.

(iv) *Reporting Requirements.* (A) A study plan shall be submitted at least 90 days before the initiation of the study. The following information shall be included: identification of the sponsor and the testing facility; qualifications and training of the personnel involved with the study; a detailed study protocol; and dates for initiation and completion of major phases of the subchronic study along with a schedule for the submission of interim and final reports.

(B) An interim summary report containing a statistical analysis of all of the test results and histopathology data shall be submitted to EPA within 30 days of completion of each testing sequence.

(C) The Final Report shall be submitted to EPA no later than 23 months after the effective date of the final test rule. This report shall include a summary and analysis of all test results including electrocardiograms, hemodynamic parameters, biochemical tests, behavioral changes, and histopathology, from each testing sequence as well as an overall summary and interpretation of the data. In addition, verified copies of all raw data such as laboratory notebooks and EKG recordings shall be submitted to the Agency with the final report.

(3) *Reproductive effects*—(i) *Required testing.* (A) Testing for reproductive

effects shall be performed in accordance with the test standard in § 772.116–3 of this chapter.

(B) The route of administraion shall be inhalation.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA at least 90-days prior to the start of testing.

(B) Interim Quarterly Summary Reports shall be submitted to the EPA during the test period.

(C) The Final Report shall be submitted to EPA no later than 30 months after the effective date of this test rule.

(d) *Environmental effects and fate testing*—(1) *Aquatic vertebrates—chronic toxicity*—(i) *Required testing.* Early life stage toxicity tests on the fathead minnow (*Pimephales promelas* Rafinesque), rainbow trout, (*Salmo gairdneri*) and sheepshead minnow (*Cyprinodon variegatus*), shall be performed in accordance with the test standard in [insert CFR # when available].

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 12 months after the effective date of this rule.

(2) *Aquatic invertebrates—chronic toxicity*—(i) *Required testing.* Flow-through life cycle toxicity tests on *Daphnia magna* or *Daphnia pulex* and on *Mysidopsis bahia* shall be performed in accordance with the test standards in [insert CFR # when available].

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 12 months after the effective date of this rule.

(3) *Birds—acute toxicity*—(i) *Required testing.* (A) Single oral dose acute toxicity tests on two species of birds shall be performed in accordance with the proposed FIFRA guidelines in § 163.71–1 of this chapter.

(B) An acute oral LD_{50} must be calculated or extrapolated in addition to determination of an LD_{50}.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 12 months after the effective date of this rule.

(4) *Birds—chronic toxicity*—(i) *Required testing.* (A) Bird reproduction tests on two species of birds shall be performed in accordance with the test standard in [insert CFR # when available].

(B) Dose level selection must be as follows:

High Dose (ppm)—0.125 × LD_{50} (in mg/kg) obtained in single oral does acute bird toxicity test

Medium dose (ppm)—0.167 × high dose

Low dose (ppm)—0.28 × high dose

(c) The following special procedures must be followed for diet preparation.

(*1*) The time over which 25 percent loss of test substance from the diet occurs must be determined. The treated diet offered to test birds must then be replaced at a frequency so that there will not be more than a 25 percent reduction from initial concentrations.

(*2*) To meet the above requirement, it is suggested that corn oil be used as a test substance carrier because it is likely to reduce loss from volatilization. Also, care should be taken at the end of each day to ensure that birds do not have the opportunity to eat treated diets that may lose more than 25 percent of the test substance before the next replacement.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 15 months after the effective date of this rule.

(5) *Terrestrial plants—early seedling growth*—(i) *Required testing.* (A) Early seedling growth tests shall be performed in accordance with the test standard in [insert CFR # when available].

(B) The test shall be performed twice for each species, once using the foliar route of exposure and once using the nutrient medium as the route of exposure.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted no later than 12 months after the effective date of this rule.

(6) *Bioconcentration—plant uptake/translocation*—(i) *Required testing.* (A) A plant uptake/translocation test shall be performed in accordance with the test standard in [insert CFR # when available].

(B) Testing is required on a minimum of two species—the most sensitive monocot and the most sensitive dicot as determined in the early seedling growth test required in paragraph (d)(5) of this section. Testing of more species is recommended but not required.

(c) The test shall be performed twice for each species, once using the foliar route of exposure and once using the nutrient medium as the route of exposure.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted no later than 15 months after the effective date of this rule.

(7) *Bioconcentration — aquatic vertebrates*—(i) *Required testing.* A bioconcentration test shall be performed in accordance with the test standard in [insert CFR # when available].

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted no later than 12 months after the effective date of this rule.

§ 773.3050 Nitrobenzene.

(a) *Identification of test substance.* (1) Nitrobenzene (CAS No. 98–95–3, also known as nitrobenzol and oil of mirbane) shall be testing in accordance with the Part.

(2) Nitrobenzene of at least 99.9 percent purity shall be used as the test substance in all of these tests.

(b) *Persons required to test.* (1) All persons who manufacture, process, or intend to manufacture or process nitrobenzene from (effective date of the rule) to (five years from the date the last final report is due) shall conduct tests and submit data as specified by this Part.

(2) Any person subject to the requirements of this section may apply to EPA for an exemption from testing pursuant to Subpart E of Part 770 of this chapter.

(c) *Health effects testing*—(1) *Reproductive effects*—(i) *Required testing.* (A) Testing for reproductive effects on one rodent species shall be performed in accordance with the test standard § 772.116–3 of this chapter.

(B) The route of administration shall be inhalation.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA at least 90 days prior to the start of testing.

(B) Interim Quarterly Summary Reports shall be submitted to EPA during the test period.

(C) The Final Report shall be submitted to EPA no later than 30 months after the effective date of this rule.

(2) *Structural teratogenic effects*—(i) *Required testing.* (A) A test for structural teratogenicity shall be conducted on nitrobenzene in accordance with the test standard in § 772.116–2 of this chapter. The rat and one other species shall be tested.

(B) The route of administration shall be inhalation.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation of the testing.

(B) No interim summary reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

(d) *Environmental effects and fate testing*—(1) *Aquatic vetebrates—acute toxicity*—(i) *Required testing.* A static acute toxicity test on the rainbow trout (*Salmo gairdneri*) shall be performed in accordance with the test standard (insert CFR # when available).

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted no later than 12 months after the effective date of this rule.

(2) *Aquatic vertebrates—chronic toxicity*—(i) *Required testing.* (A) Early life stage toxicity tests on the rainbow trout (*Salmo gairdneri*), fathead minnow (*Pimephales promelas* Rafinesque) and sheepshead minnow (*Cyprinodon variegatus*), shall be preformed in accordance with the test standard in (insert CFR # when available).

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

(3) *Aquatic invertebrates—chronic toxicity*—(i) *Required testing.* (A) A static renewal life cycle test on *Daphnia magna* or *Daphnia pulex* and a flow-through life cycle test on *Mysidopsis bahia* shall be performed in accordance with the test standard in (insert CFR # when available).

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

(4) *Birds—acute toxicity*—(i) *Required testing.* (A) Single oral dose acute toxicity tests on two species of birds shall be performed in accordance with the proposed FIFRA guidelines under § 163.71–1 of this chapter.

(B) An acute oral LD_{10} must be calculated or extrapolated in addition to determination of an LD_{50}.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

(5) *Birds—chronic toxicity*—(i) *Required testing.* (A) Bird reproduction tests on two species of birds shall be performed in accordance with the test standard in (CFR # when available).

(B) Dose level selection must be as follows:

High dose (ppm)—0.125 × LD_{10} (in mg/kg) obtained in the single oral dose acute bird toxicity test

Medium dose (ppm)—0.167 × high dose

Low dose (ppm)—0.028 × high dose

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 15 months after the effective date of this rule.

(6) *Terrestrial plants—early seedling growth, seed germination/root elongation.* (i) *Required testing.* (A) Early seedling growth and seed germination/root elongation tests shall be performed in accordance with the test standards in (insert CFR # when available).

(B) The early seedling growth test shall be performed twice for each species, once using the foliar route of exposure and once using the nutrient medium as the route of exposure.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

(7) *Bioconcentration—plant uptake/translocation*—(i) *Required testing.* (A) A plant uptake/translocation test shall be performed in accordance with the test standard in (insert CFR # when available).

(B) Testing is required on a minimum of two species—the most sensitive monocot and the most sensitive dicot as determined in the early seedling growth test required in paragraph (d)(7) of this section.

(C) The test shall be performed twice for each species, once using the foliar route of exposure and once using the nutrient medium as the route of exposure.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted no later than 15 months after the effective date of this rule.

(8) *Soil adsorption*—(i) *Required testing.* (A) Testing for soil adsorption shall be conducted in accordance with the test standard in § 772.122–5 of this chapter.

(B) At least one soil from each of the following soil orders must be used in the soil thin-layer chromatography test method: Alfisol, Inceptisol, Mollisol, and Vetisol. Each soil must have: an organic matter content between one and four percent; a pH between five and seven; and a cation exchange capacity between 7 and 25 meg/100g. At least one soil must have Kaolinite as its dominant clay mineral; in addition, the other soils must have illite or montmorillonite as the dominant clay mineral. Also, at least one soil must have a redox potential more negative than −185mV.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of testing.

(B) No interim reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

§ 773.4400 1,1,1-Trichloroethane.

(a) *Identification of test substance.* (1) 1,1,1-Trichloroethane (CAS NO. 71–55–6, also known as methyl chloroform) shall be tested in accordance with this Part.

(2) 1,1,1-Trichloroethane stabilized with 0.5 percent butylene oxide shall be used as the test substance in all tests.

(b) *Persons required to test.* (1) All persons who manufacture, process or intend to manufacture or process 1,1,1-trichloroethane from (effective date of the rule) to (5 years from the date the last final report is due) shall conduct tests and submit data as specified by this Part.

(2) Any person subject to the requirements of this Section may apply to EPA for an exemption from testing pursuant to Subpart E of Part 770.

(c) *Health effects testing*—(1) *Structural teratogenic effects*—(i) *Required testing.* (A) A test for structural teratogenicity shall be performed in accordance with the test standards in § 772.116-2 of this chapter.

(B) The route of administration shall be inhalation.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to EPA no later than 12 months after the effective date of this rule.

(d) *Environmental effects and fate testing*—(1) *Aquatic vertebrates—acute toxicity.* (i) *Required testing.* (A) A flow-through acute toxicity test on the rainbow trout (*Salmo gairdneri*) shall be performed in accordance with the test standard in [insert CFR # when available].

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 12 months after the effective date of this rule.

(2) *Aquatic vertebrates—chronic toxicity tests*—(i) *Required testing.* (A) Early life stage toxicity tests on the fathead minnow (*Pimephales promelas* Rafineque), rainbow trout (*Salmo gairdneir*), and sheepshead minnow (*Cyprinodon variegatus*), shall be performed in accordance with the test standard in [insert CFR# when available].

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 12 months after the effective date of this rule.

(3) *Aquatic invertebrates—chronic toxicity*—(i) *Required testing.* (A) Flow-through life cycle tests on *Daphnia magna* or *Daphnia pulex* and on *Mysidopsis bahia* shall be performed in accordance with the test standard in [insert CFR# when available].

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 12 months after the effective date of this rule.

(4) *Birds—chronic toxicity*—(i) *Required testing.* (A) Bird reproduction tests on two species of birds shall be performed in accordance with the test standard in [insert CFR# when available].

(B) Dose level selection must be as follows:

High dose (ppm)—0.125 × 250 (mg/kg)
Medium dose (ppm)—0.167 × high dose
Low dose (ppm)—0.028 × high dose

(C) Special procedures must be followed for diet preparation:

(*1*) The time over which 25 percent loss of test substance from the diet occurs must be determined. The treated diet offered to test birds must then be replaced at a frequency so that there will not be more than a 25 percent reduction from initial concentrations.

(*2*) To meet the above requirement, it is suggested that corn oil be used as a test substance carrier because it is likely to reduce loss from volatilization. Also, care should be taken at the end of each day to ensure that birds do not have the opportunity to eat treated diets that lose more than 25 percent of the test substance before the next replacement.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted to the EPA no later than 15 months after the effective date of this rule.

(5) Terrestrial plants—early seedling growth, seed germination/root elongation—(i) *Required testing.* (A) Early seedling growth and seed germination/root elongation tests shall be performed in accordance with the test standards in [insert CFR #'s when available].

(B) The early seedling growth test shall be performed twice for each species, one using the foliar route of exposure and once using the nutrient medium as the route of exposure.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later tha the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted no later than 12 months after the effective date of this rule.

(6) *Bioconcentration—plant uptake and translocation*—(i) *Required testing.* (A) A plant uptake/translocation test shall be performed in accordance with the test standard in [insert CFR# when available]. Testing is required on a minimum of two species—the most sensitive monocot and the most sentitive dicot as determined in the early seedling growth test required in paragraph (d)(5) of this section.

(B) The test shall be performed twice for each species, once using the foliar route of exposure and once using the nutrient medium as the route of exposure.

(ii) *Reporting requirements.* (A) The Study Plan shall be submitted to the EPA no later than the initiation date of the test.

(B) No interim reports are required.

(C) The Final Report shall be submitted no later than 15 months after the effective date of this rule.

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